



# ACTA MEDICA SCANDINAVICA

\*

## REDACTORES

ERIK ASK-UPMARK UPSALA	G. BERGMARK UPSALA	H. I. BING KÖBENHAVN	BERTEL VON BONSDORFF HELSINGFORS
R. EHRSTRÖM HELSINGFORS	K. PABER KÖBENHAVN	OLAV HANSEN OSLO	ÖSTEN HOLSTI HELSINGFORS
C. HOLTEN AARIUS	LAURI KALAJA ÅBO	WILLIAM KERPPOLA HELSINGFORS	ANDERS KRISTENSON STOCKHOLM
HAQVIN MALMROS LUND	CARL MÜLLER OSLO	EGGERT MÖLLER KÖBENHAVN	MARTIN ODIN GÖTEBORG
F. SALTZMAN HELSINGFORS	H. A. SALVESEN OSLO	JÖN H. SIGURDSSON REYKJAVIK	NANNA SVARTZ STOCKHOLM
HANS JACOB USTVEDT OSLO	JAN WALDENSTRÖM MÅLMÖ	ERIK WAERBURG KÖBENHAVN	
J. G. G. BORST AMSTERDAM	F. S. P. VAN BUCHEM GRÖNINGEN	P. FORMINE AMSTERDAM	
C. D. DE LANGEN UTRECHT	J. MULDER LEYDEN		

## EDITOR

I. HOLMGREN  
STOCKHOLM

## COLLABORANT:

- IN DANIA: S. Bang, H. C. Gram, Poul Iversen, Aage Th. Jacobsen, Ejnar Jarlov, E. Meulegracht, Otto Moltke, A. Norgaard, An. Nyfeldt, K. Schroeder, K. Secher.
- IN FINNIA: Erik Adlercreutz, Pekka Brummer, Mons-Christian Ehrström, Martti Hirvonen, Martin Savolin, Pauli Soisalo, Guido Tötterman, I. Vartiainen, J. Wahlberg, E. A. v. Willebrand.
- IN HOLLANDIA:
- IN NORVEGIA: Olaf Bang, Gunnar Bøe, R. Hatlehol, Fr. Harbütz, H. F. Host, Anton Jervell, G. H. Monrad-Krohn, K. Motzfeldt, Olaf Rømerke.
- IN SUEGIA: Hilding Berglund, Stig Björkman, Leonard Brahmé, Gustaf Brun, Arthur Engel, Birger Enoeksson, Claes Grill, A. Gullbring, Sixten Hesser, G. Kahlmeter, Kj. O. af Klercker, Oscar Lindbom, Malte Ljungdahl, Gustav Nylin, Ernst Sahlgren, Ernst B. Salén, Elsa Segerdahl, Birger Strandell, J. Tillgren, Erik Wassén, A. Westergren, H. Öhnell.

ACTA MEDICA SCANDINAVICA'S FÖRLAG, STOCKHOLM

A



30314.

# INDEX

Vol. CXXXVI.

	Pag.
J. R. BORST (The Hague, The Netherlands): Disturbances in water- and salt metabolism in the final stage of chronic renal insufficiency .....	1
EBBE NYMAN (Stockholm): Does human blood contain appreciable amounts of atropinesterase? .....	9
E. DONZELOT, AM. EMAM-ZADE, R. HEIM DE BALSAC & C. METIANU (Paris): Quelques considérations sur la lèvocardie et présentation de 2 cas personnels .....	13
C. A. HERNBERG and WALTER EDGREN (Helsingfors): Looser-Milkman's syndrome with neurofibromatosis Recklinghausen and general decalcification of the skeleton .....	26
BRYAN FABRICIUS (Copenhagen): Combined kymographic and electrocardiographic studies of the duration of the presphygmic period .....	34
GUNNAR LINDGREN (Stockholm): Macrocytosis in acute hepatitis and pernicious anemia. A comparison based on 830 Price-Jones' curves .....	39
ARNE P. SKOUBY (Copenhagen): Scleroderma-like picture following a single serum injection .....	51
OLOF LJUNG (Stockholm): The electrocardiogram in hypocalcemia with special reference to the T-wave .....	56
GUNNAR BERG (Oldesloe, Deutschland): Nekrotisierende Jejunitis .....	71
S. BONFILS et A. LAMBLING (Paris): Études des troubles du métabolisme des hydrates de carbone au cours des diarrhées chroniques dites banales .....	79
STINA BJÖRK and KNUT LIEDHOLM (Lund, Sweden): The femoral pulse curve in coarctation of the aorta .....	97
V. K. SUMMERS (Liverpool, England): The rôle of the adrenal cortex and gonads in the control of sexual hair distribution .....	105
PER HANSSEN (Oslo): The incidence of auricular flutter and auricular fibrillation associated with complete auriculo-ventricular dissociation .....	112
OLE STORSTEIN (Bergen, Norway): Measurement of the venous pressure and of the circulation time .....	122
VOJTĚCH HOENIG (Prague): Sur l'élimination urinaire de la quinine dans les hépatopathies .....	130
W. PAOLINO (Turin, Italy): Variations of the mean diameter in the ripening of the erythrocyte .....	141
SVEN JOHNSSON (Hälsingborg, Sweden): Acute myeloblastic leukemia and insufficiency of the bone marrow .....	148
E. DONZELOT, A. M. EMAM-ZADE, R. HEIM DE BALSAC et C. METIANU (Paris): Étude des tracés électrocardiographiques de 314 cardiopathies congénitales .....	159
J. K. V. VAN DOMMELEN and C. FRANCKE (The Hague): Thymol and dilution turbidity tests, their relation to the gamma-globulin content of the serum and the morphology of the liver parenchyma .....	177

GUNNAR BAUER, HARRY BOSTRÖM, ERIK JORPES and SIXTEN KALLNER (Stockholm): Intramuscular administration of heparin .....	188
TAGE HILDEN (Copenhagen): Hypertensive encephalopathy associated with hypochloremia .....	199
AAGE VIDEBAEK (Copenhagen): The course and prognosis of Hodgkin's disease ...	203
FRANCESCO ZINI (Florence, Italy): Concentrations of dihydrostreptomycin in blood, serum and urine, increased by solution in procain-pectine .....	209
ALVAR GJERTZ (Stockholm): Some technical points on the measurement of skin temperature with thermocouples .....	214
ROBERT LIEFMANN (Stockholm): Endocrine imbalance in rheumatoid arthritis and rheumatoid spondylitis: hyperglycemia unresponsiveness, insulin resistance, increased gluconeogenesis and mesenchymal tissue degeneration .....	226
STEN BRATTSTRÖM (Hälsingborg, Sweden): On the need for more far-reaching indications for operation in cases of ventricular ulceration .....	233
SVEN LÖFGREN (Stockholm): Age distribution of erythema nodosum .....	241
MARIO STEFANINI (Milwaukee, U. S. A.): Studies on the rôle of calcium in the coagulation of blood .....	250
J. A. BARCLAY, W. T. COOKE and G. DE MURALT (Birmingham, Great Britain): An investigation of the hypothesis of tubular excretory mass, $T_m$ .....	267
FREDERIC DURAN-JORDA (Manchester, Great Britain): The secretion of reticulocytes by the normoblast .....	275
H. C. BURGER and F. L. J. JORDAN (Utrecht, Holland): The influence of distance on the pitch of the percussion note .....	283
M. BJORNEBOE, CHR. HAMBURGER and M. JERSILD (Copenhagen): Steroid hormones in hepatitis .....	287
OLOF LJUNG (Stockholm): Zur Frage des verlängerten QT .....	293
K. ALBERTSEN, N. R. CHRISTOFFERSEN and F. HEINTZELMANN (Copenhagen): The examination of isolated serum proteins by the mercuric chloride and thymol reactions .....	302
K. ALBERTSEN and F. HEINTZELMANN (Copenhagen): Mercuric chloride and thymol precipitation in plasma and serum .....	313
K. ALBERTSEN and F. HEINTZELMANN (Copenhagen): The influence of heparin on the precipitation of serum proteins by mercuric chloride and thymol .....	316
OLOF FORSSMAN and HANS STENQVIST (Hälsingborg, Sweden): Paroxysmal tachycardia which the patient was momentarily able to produce himself .....	323
VIKTOR GAUSTAD and JOHAN HERTZBERG (Oslo): Acute necrosis of the renal papillae in pyelonephritis; particularly in diabetics .....	331
SVEN BERGQVIST (Stockholm): Observations concerning the presence of pyogenic staphylococci in the nose and their relationship to the antistaphylolysin titre ..	343
LEOPOLD EPSTEIN and ASGER NØRHOLM-PEDERSEN (Aarhus, Denmark): Treatment with dicumarol in small continuous doses .....	351
NILS ALWALL, CURT EKELOUND and LEO ORAS (Lund, Sweden): Inter-capillary glomerulosclerosis .....	359
GUNNAR VETNE (Stavanger, Norway): Lupus erythematosus disseminatus .....	371
CARSTEN MÜLLER (Oslo): Periarteritis nodosa — asthma bronchiale — iododerma tuberosum .....	378
FREDRIK SALTZMAN and HENRIK BORGSTRÖM (Helsingfors): Multiple plasmocytoma treated with urethane .....	388
HEMNING ENGELUND POULSEN (Copenhagen): Basophilic stippling of the red blood corpuscles during chrysotherapy .....	393
EINO KULONEN (Helsingfors): On hyaluronidase inhibitors in human blood .....	401

VAGN SCHMIDT (Copenhagen): The significance of the Exton-Rose tolerance test for the diagnosis of diabetes mellitus .....	408
A. ARENDS (Groningen, The Netherlands): Blood disease and the so-called generalised non-reactive tuberculosis .....	417
CARL CÖSTER (Nynäshamn, Sweden): Streptococcus agglutination in cases of chronic polyarthritis .....	430
M. FÖLDI, ST. LAZAROVITS und G. SZABÓ (Budapest): TmNII <sub>4</sub> ; Beziehungen zwischen renalen Synthesen und anderen Tubularfunktionen .....	439
TORSTEN LINDQVIST (Gothenburg, Sweden): Intermittent claudication and vascular spasm. III .....	447
ANTON FLOYSTRUP and ARNE P. SKOUBY (Copenhagen): Investigations upon the mechanism of indirect warming .....	466

*Book reviews:*

WOLFRAM KOCK (Stockholm): E. Berghoff: Festschrift zum 80. Geburtstag Max Neuburgers .....	157
JAN MELLGREN (Lund, Sweden): Folke Henschen: Morgagni's syndrome .....	238
N. G. NORDENSON (Stockholm): E. S. Sanmartino et collab.: Tratado practico de hemoterapia .....	397
N. G. NORDENSON (Stockholm): M. Ninni: I reticulociti .....	398
ALF GULLBRING (Stockholm): Hermann Weber: Die Komplettierung des insuffizienten Pneumothorax .....	399
HJALMAR HOLMGREN (Stockholm): Lea del Bo Rossi: Il sistema nervoso studiato con una nuova tecnica .....	473
PHILIPP SCHNEIDER (Stockholm): F. Feyrter: Über die Anzeigepflicht des Prosektors wegen ärztlichen Verschuldens .....	474

Index to supplementary volumes 201—235 .....	475
--	-----

Supplementum CCXXXIII (233), ALF TELLEFSEN (Stord, Norwegen): Über die Rheumatismusbordität durch Krankenkassenmaterial beleuchtet.

Supplementum CCXXXIV (234), Papers dedicated to Dr. POUL IVERSEN on his sixtieth birthday November 20, 1949.

Supplementum CCXXXV (235), BENGT SKANSE (Stockholm): Radioactive iodine in the diagnosis of thyroid disease.



Landis, Elsom, Bott and Shields demonstrated in 1935 that under the influence of a limited salt intake in the diet of patients suffering from nephrosclerosis or chronic glomerulonephritis, the urea and creatinine clearances fell, while the blood urea and non-protein-nitrogen concentrations rose. If the excessive loss of salt in the urine was compensated for by the administration of sufficiently large amounts of NaCl, then the clearance rose and the blood serum urea and non-protein-nitrogen concentrations fell. It is important, also, in cases of acidotic uremia to commence as early as possible with the administration of sodium bicarbonate or sodium lactate in large doses. (De Langen and others.) Acidosis increases to an appreciable extent the dehydration and loss of salt and chloride in the urine, especially in patients with chronic renal insufficiency. The excretion of salt in such cases is, nevertheless, never very great as a rule, and extreme degrees of dehydration occur but seldom if the patients are not severely restricted in the intake of salt, and if they do not vomit. The following report by Thorn, Koepf and Clinton is therefore worthy of mention.

These authors presented the case-histories of two young uremic patients suffering from chronic nephritis and chronic nephritis in the presence of cystic disease of the kidneys respectively. In both cases the renal disturbances led to a severe state of dehydration, hypochloremia, hyponatremia and acidosis, with hemoconcentration and hypotension. Both were admitted to hospital in a shock-like condition and it was at first thought that they were suffering from acute suprarenal failure. Intramuscular injection of large amounts of desoxycorticosterone acetate were found to have no effect on the disturbed water and salt metabolism, while the suprarenal glands were seen at autopsy to be intact. After the intravenous infusion of isotonic NaCl and glucose solutions the high blood urea concentration decreased, in spite of a kidney function of between 5 and 15 % of normal. (Case I, Thorn *et al.*) Both patients remained in an excellent state of health for a number of years, due to the daily addition to the food of 10—20 g NaCl and 5—10 g sodium bicarbonate. By this means dehydration and acidosis were prevented, while on the other hand the blood pressure remained normal and no oedema developed. The syndrome described, with alterations in water and salt balance, was, for the sake of brevity, given the name by Thorn and his colleagues, of »salt-losing nephritis».

We give now the case-history of a 42-year-old man suffering from chronic renal insufficiency and uremia, caused by bilateral cystic disease of the kidneys, and in whom, as in the two cases of Thorn and co-workers, significant changes were present in the metabolism of water and salt.

A man of 42 years, who had previously never had any illness of importance, had complained for 1½ years of tiredness, loss of weight, cramps in the calves, poor appetite and a severe thirst. On Dec. 4 he consulted us for the first time. General physical examination revealed nothing abnormal, except for a somewhat dry, scale skin. Blood pressure: 140/100 mm Hg; hypochromic anemia, hemoglobin: 56 %; erythrocytes: 3,920,000/mm<sup>3</sup>; leucocytes: 7,200 mm<sup>3</sup>; differential count: segmented neutrophils: 76 %, eosinophils: 3 %, lymphocytes: 18 %, and monocytes: 3 %. The blood sedimentation rate was greatly raised, 58 and 82 mm in 1 and 2 hours resp. In the urine the reactions for albumen, glucose and acetone were negative; urinary sediment showed no abnormalities. Thorax

X-ray: nothing abnormal. On Feb. 17, 1947 the patient reported again. His complaints had remained unchanged and his appetite was now very poor. B. S. R.: 69 and 86 mm in 1 and 2 hours; hemoglobin: 66 %; erythrocytes: 4,100,000/mm<sup>3</sup>. We may already note here that during the subsequent course of the illness *daily examination of the urine never showed any abnormality of significance*. The urine contained at the most a trace of albumen, and in the sediment there were never more than a few leucocytes and occasionally asporadic erythrocyte.

On Feb. 18 the patient complained of nausea, the next morning he began to vomit, that evening he was apathetic and somnolent, and on Feb. 20 he was admitted to hospital as an emergency case.

*Examination:* Patient is apathetic and disorientated. From time to time he vomits greenish fluid. Obvious hyperpnoea. Tongue is dry and coated. Skin is dry, wrinkled and scaly, and skin folds do not disappear. Also, now and again muscle contractions and cramps in arms and legs. Temp.: 36.5 C (98.2 F). Blood pressure: 130/80 mm Hg. Percussion and auscultation of heart and lungs show no abnormality. Liver and spleen not enlarged, and the kidneys are not palpable. Ophthalmoscopic examination: fundi appear normal. Hemoglobin: 90 %; erythrocytes: 4,500,000/mm<sup>3</sup>. Serum specific gravity (copper sulphate method): 1.034; total serum protein: 10.42 g %; serum albumen: 7.70 g %; serum globulin: 2.72 g %; non-protein-nitrogen in the serum: 273 mg %; blood urea: 583 mg % (Ambard); serum chlorides: 304.5 mg % (86 m.eq./litre); serum sodium: 289 mg % (126 m.eq./litre); serum potassium: 16.9 mg % (4.3 m.eq./litre); specific gravity of the urine: 1.007, and the NaCl concentration in the urine was 4 g/litre.

The above laboratory findings point, in the first place, to a marked hemoconcentration, i. e. high serum specific gravity, 1.034, high total protein content of the serum, and especially the high serum albumen (7.70 g %), while the hemoglobin had risen in a few days from 66 % to 90 %. During treatment of the dehydration by intravenous infusion of physiological saline the hemoglobin fell rapidly from 90 % (on Feb. 21) to 55 % (on Feb. 27), with 2,600,000 red cells/mm<sup>3</sup>. At the same time the specific gravity of the serum fell from 1.034 to 1.023. It thus seemed probable that the high blood urea concentration was largely attributable to a functional disturbance of renal function, as a result of dehydration with hypochloremia, hyponatremia and acidosis. It is unfortunate that during the first few days after the admission of the patient to hospital it was omitted to determine the alkali reserve in the serum; this was later found to be appreciably lowered.

For some days there was no question of feeding the vomiting, apathetic patient by mouth, and we were compelled to employ the parenteral route for the giving of fluid, minerals and calories. Shortly after admission intravenous and subcutaneous infusions were commenced, with isotonic NaCl solution, Ringer's solution and 5 % glucose solution. When it was obvious that the intravenous infusion was being well tolerated, without any indication that the blood pressure would rise, and without formation of oedema, or development of a raised venous pressure, larger amounts of fluid were given, until for some days between 8,000 and 11,000 ml of salt-glucose solution were given intravenously each day. The glucose in the mixture played a not insignificant part in the meeting of caloric requirements. (Fig.) On the 5th and 14th days, 13 and 17 litres respectively were infused, containing 134 and 110 g NaCl resp. (Table.) The chloride, sodium and total base concentrations (a) in the serum rose, although the values remained consistently below normal. The skin was less dry, but the blood pressure failed to rise, remaining between 100/60 and 120/80 mm Hg. Satisfactory amounts of urea were excreted in the urine, up to a maximum of 51 g of urea ( $\pm$  24 g urea nitrogen) in 9,500 ml urine in 24

- (a) Electrolytic estimation of the total base concentration in the serum, using a modified method of H. Nielsen (normal conc.:  $\pm$  155 m.eq./litre) and carried out in the laboratory of the Gemeenteapotheek, by Dr. C. L. Harders.

Table.

*Intake (per os, intravenously and subcutaneously) and urinary output of water and chloride (as NaCl) over a 23 days period.*

Date	Days after admission	Intake per 24 hours		Urinary output per 24 hours	
		NaCl in g	Water in ml	Chloride (NaCl in g)	Water in ml
24. II.	5	134	13,300	63	
25. II.	6	63	10,200	75	9,750
26. II.	7	61.5	9,500	62	9,500
27. II.	8	31.5	6,750	44	8,300
28. II.	9	17	10,350	29	5,700
1. III.	10	2	500	19	4,300
2. III.	11	54	10,350	42	3,700
3. III.	12	62	10,100	57	7,250
4. III.	13	2	1,900	17	8,500
5. III.	14	110	17,000	49	3,100
6. III.	15	64	10,450	62	10,000
7. III.	16	2	2,200	23	9,200
8. III.	17	54	8,600	48	4,100
9. III.	18	56	10,850	54	7,500
10. III.	19	3	2,300	14	8,200
11. III.	20	3	2,950	18	2,300
12. III.	21	5	2,800	14	3,300
13. III.	22	5	2,100	12	2,300
14. III.	23	85	12,600	42	2,400
15. III.	24	39	8,600	52	6,650
16. III.	25	3	1,700	25	8,000
17. III.	26	3	1,800	16	3,800
18. III.	27	3	2,400	11	2,800
Total intake and urinary output in 23 days		± 862	159,200	± 850	132,500

Approximate mean difference between water intake and urinary water output:

$$\frac{159,200 - 132,500}{23} = 1,160 \text{ ml per day}$$

Approximate mean difference between NaCl intake and urinary NaCl output:

$$\frac{862 - 850}{23} = 0.52 \text{ g NaCl per day.}$$

hours, (b). The blood urea concentration (c), which had been 583 mg % on the first day, and which had risen by the following day to more than 600 mg %, fell rapidly with treatment, although it continued to vary at a still dangerously high level, between 170 and 280 mg % (Fig.). If the intravenous infusion of fluid was stopped for several days, then there followed quickly dehydration and a rapid rise in the blood urea.

The table shows the amounts of water and chloride (expressed as NaCl) which were given (per os, subcutaneously and intravenously), and excreted in the urine, day by day over a period of 23 days. In this period an average of 1,160 ml of fluid was given above

- (b) In the estimation of the urea conc. in the urine by Ambard's method, the amount of ammonia is at the same time measured. Reference here to excretion of urea in the urine includes thus the excretion of ammonia, *i. e.* urea + ammonia.
- (c) The urea concentration in the serum was determined by the method of Conway-Lips; only the first few determinations were by means of the Ambard method.

the amount excreted. This difference may be shown by calculation to be due to the loss of moisture from the skin and from the respiratory tract. The estimation of the chloride content of the urine by means of the chlorometer of Strauss yields results which are only approximately correct; the salt balance in the table is thus not absolutely accurate. It is nevertheless obvious from the table that the great quantities of water and NaCl which were administered to this patient during the 23-day period, were practically completely and almost immediately excreted in the urine, in spite of a renal function of even less than 10 % of normal. There was no retention of water and the above findings indicate that there was but a slight retention of sodium chloride.

During the first weeks of March his general state was fairly good, and his appetite considerably improved. He was obviously hyperpnoeic. Temperature subfebrile, blood pressure between 100/60 and 120/80 mm Hg. After several blood transfusions the hemoglobin rose to 77 %. B. S. R. 81 mm in the first hour. Serum sodium low, 295 mg % (128 m.eq./litre); serum potassium: 17 mg % (4.35 m.eq./litre); serum alkali-reserve markedly lowered: 25.5 and 29 vol. CO<sub>2</sub> % (11.5 to 12.5 m.eq./litre); serum calcium very low: 5.1 mg % (2.55 m.eq./litre); inorganic phosphates in the plasma: 9.0 mg %; serum non-protein-nitrogen: 106 to 124 mg %; serum urea concentration: 165 to 205 mg %.

Urine: 2,400 to 10,000 ml per day. S. g. 1,005—1,007. Urinary urea concentration: 2.5 to 5.75 g/litre; excretion of ammonia: 0.160 to 0.500 g per day; urinary chloride concentration (expressed as NaCl) 5 to 8 g/litre (15 to 63 g per 24 hours). Urea Clearance (maximum clearance): 5.5 to 11 %.

Patient obtained 1,500 to 2,500 cals. and 20 to 40 g of protein daily.

The hyperpnoea and the low alkali reserve point to an acidosis. After intravenous injection of calcium gluconate and administration of calcium lactate orally (6 g daily) the serum calcium concentration rose slowly to normal levels. In order to raise the low alkali reserve large amounts of sodium bicarbonate were necessary — in the course of eight days the patient received 210 g of bicarbonate, after which the alkali reserve in the serum had risen to 55.5 and 61 vol. CO<sub>2</sub> % (25 and 27.5 m.eq./litre); serum chloride: 352 mg % (99.5 m.eq./litre); total base in the serum: 153 and 154 m.eq./litre.

As the dehydration and acidosis had disappeared, the serum urea concentration fell to 130 mg % (March 26). The intravenous infusions were stopped, and the temperature fell to normal.

From March 27 until April 11 a high caloric, protein-poor diet was given. This diet, (see Borst, J. G. G.) contained 2.2 g of protein and provided 3,000 calories per day. Furthermore, 10 to 15 g NaCl, 6 g sodium bicarbonate and 3 g calcium lactate were given daily, and care was taken that the patient obtained sufficient fluid and adequate amounts of the various vitamins. At the beginning of April the patient was mobilised. Blood pressure: 100/70 mm Hg to 120/80 mm Hg; hemoglobin: 80 % and 4,000,000 erythrocytes per mm<sup>3</sup>. B. S. R.: fallen to 19 and 26 mm in 1 and 2 hours resp.

The mineral spectrum of the blood was now more or less normal and the serum urea concentration had fallen to 38 and 44 mg % (Fig.). Diuresis: 4,000 to 4,500 ml per 24 hours; the total excretion of urea nitrogen in the urine measured only 1.9 to 3.5 g per 24 hours. As a result of the high caloric and practically protein-free diet the endogenous breakdown of protein and production of urea fell to minimal levels (see Fig.). The nitrogen balance would have been certainly negative during this period of 14 days, when no blood transfusions had been given. Urea clearance: 8.5 to 13.0 of normal; phenolsulphonphthalein excretion test: 7 % of the injected quantity was excreted in 2 hours.

We expected that our patient would soon be able to leave hospital. With a renal function of  $\pm 10$  % it was not to be feared that uremic symptoms or signs would develop, as long as the diet was low in protein and adequate in calories, the intake of water remained high enough, and the loss of salt in the urine was compensated for by the administration of sufficient sodium chloride (10—15 g/day) and sodium bicarbonate ( $\pm 6$  g/day).

In connection with the observed disturbances in water and salt metabolism (with de-



hydration, hypochloremia, hyponatremia, acidosis and negative chloride and sodium balance) it was necessary to exclude the possibility of a simultaneous suprarenal cortex insufficiency. It was found that the intramuscular injection of large amounts of desoxycorticosterone acetate (80 mg in 5 days) exerted no influence on the excretion or retention of water, sodium or chloride by the kidneys, while the weight and blood pressure also remained constant. (See Fig.) We were thus able to assume that the production of adrenocortical hormone was not significantly interfered with in our patient.

On April 18 the temperature rose again, and on April 19 a leftsided exsudative pleurisy with hemorrhagic pericarditis were diagnosed. On May 12 there developed also a right-sided pleurisy. In the clear or hemorrhagic fluid obtained from pleural and pericardial cavities were neither tubercle bacilli nor other micro-organisms found, even by repeated examination. Cultures of these fluids were negative, as were blood cultures. Thorax photos provided no further information. Pirquet and Mantoux reactions remained negative during the whole illness.

The temperature in the subsequent five months was of high undulating type, interchanging with intermitting temperature, with short periods when there was but slight or even no temperature elevation. In spite of repeated blood transfusions the hemoglobin fell to below 50 % with a red cell count of 2,000,000 per mm<sup>3</sup>; leucocytes: 5,000 to 14,000/mm<sup>3</sup>; blood picture marked toxicity, many non segmented polymorphnuclear cells, lymphopenia and thrombocytopenia. Until shortly before the patient's death the blood urea remained below 200 mg %. On Sept. 29 he died, approximately 7 months after his admission to hospital.

*Autopsy:* Post-mortem diagnosis (Dr. P. M. Bakker, from the laboratory of Dr. R. R. Rochat): Bilateral cystic disease of the kidneys, caseous hilar lymph glands, bilateral fibrinous exudative pleurisy, tuberculous pericarditis and hematogenous miliary tuberculosis, partly necrotising.

The *spleen* weighed 610 g and showed, as did the liver and the lungs, many miliary tubercles, with only slight caseation. The liver cells showed marked fatty degeneration.

*Suprarenal glands* were normal in structure and contained but few epitheloid-cell tubercles. The cortex was intact.

Both *kidneys* were large and weighed 770 g together. On section there were innumerable cysts to be seen, from pin-head size to the size of a chestnut, filled with turbid, brown fluid, and lined with flat to cubical epithelial cells. Between the cysts was little renal parenchyma. Those glomeruli still present were microscopically almost all intact. The parenchyma showed marked connective tissue proliferation. There was evidence of severe degenerative changes in the tubules, especially in the first convoluted tubules, which were difficult to distinguish and were markedly compressed by the proliferated connective tissue. The second convoluted tubules were often considerably dilated and contained hyaline and granular material in the lumen. There was also cloudy swelling of the tubule epithelial cells.

## Discussion.

The bilateral cystic kidneys were the cause of a progressive, chronic renal insufficiency. The establishment of a diagnosis was complicated by the absence of albuminuria and of abnormalities in the urinary sediment, in spite of daily urine examination. The blood pressure was, moreover, normal or even low, and the kidneys were not palpable. In the residual renal tissue the glomeruli appeared to be practically intact; on the other hand, the tubules, especially the first convoluted tubules, showed severe degenerative changes. On the basis of these findings one could postulate that, although the glomerular activity was greatly impaired, the changes in the function of the tubules would dominate the syn-

### Summary.

Case-history of a 42-year-old man suffering from uremia, caused by bilateral cystic disease of the kidneys.

The patient was severely dehydrated. After the administration of large amounts of water and sodium chloride the urinary output rose to 10 liters of water and 75 g of NaCl per day in spite of a low plasma sodium level and an urea clearance of 8 to 10 percent of normal.

Injection of desoxycorticosterone had no effect on the sodium chloride excretion; on autopsy the suprarenal glands were found to be normal.

By the administration of a liberal amount of water and 10 to 20 g of NaCl and 3 to 10 g of NaHCO<sub>3</sub> daily dehydration could be prevented; no edema developed and the blood pressure remained normal. The use of a protein poor, high caloric diet and of large amounts of water was followed by a fall in the blood urea level from 600 to 40 mg per cent. The patient died of miliary tuberculosis 7 months after his admission to the hospital.

### Literature.

Borst, J. G. G.: Protein katabolism in uremia. Effects of protein-free diet, infections and blood-transfusions. *Lancet* I: 824—828; 1948. — Bradley, St. E.: Biochemical abnormalities during renal insufficiency. *New Engl. J. Med.* 235: 755—761; 1946 and 235: 791—797; 1946. — Landis, E. M., Elsom, K. A., Bott, P. A. and Shields, E. H.: Observations on sodium chloride restriction and urea-clearance in renal insufficiency. *J. Clin. Investig.* 14: 525; 1935. — De Langen, C. D.: De acidotische uraemie en haar behandeling. *Nederlandsch Tydschr. v. Geneesk.* 85 — IV: 3891—3896; 1941. — Magguire, W. B. Jr.: Risk of uremia due to sodium depletion. *J. A. M. A.* 137: 1377—1378; 1948. — Nielsen, H.: Elektrolytsk Totalbasebestemmelse i serum. *Nordisk Med.* 8: 1667; 1940. — Peters, J. P.: Water balance in health and disease. In Duncan's »Diseases of metabolism» pp. 271—326, 2nd Ed., W. B. Saunders Comp. 1947, Philadelphia and London. — Thorn, G. W., Koepf, G. F. and Clinton, M. Jr.: Renal failure simulating adrenocortical insufficiency. *New Engl. J. Med.*, 231: 76—85; 1944. — Winkler, A. W. and Crankshaw, O. F.: Chloride depletion in conditions other than Addison's disease. *J. Clin. Investig.*, 17: 1; 1938.

---

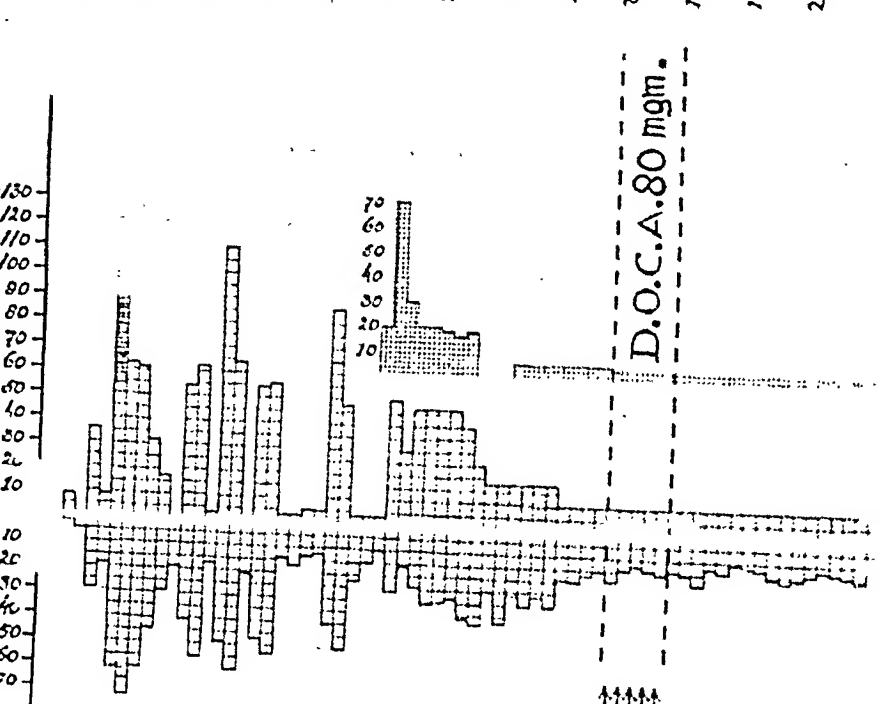
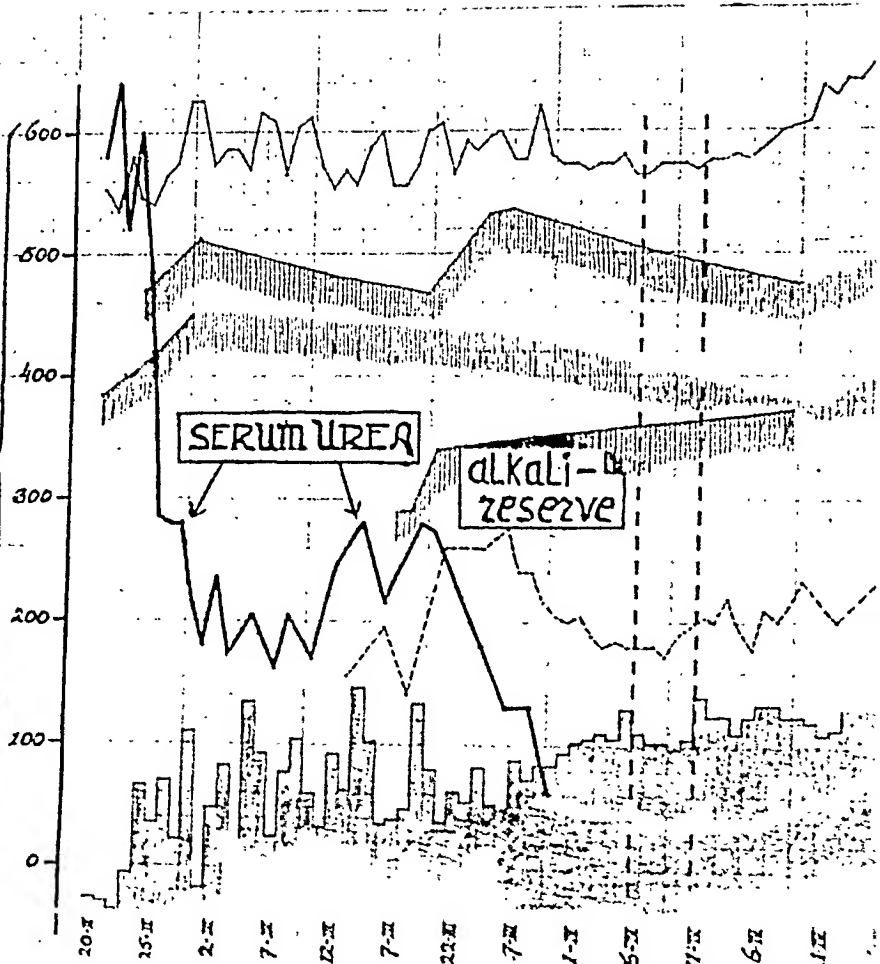
Urea concn. in serum, mgm. %

oral Nitrogen  
intake in gm.  
per 24 hrs.

UREA nitrogen + ammonia  
nitrogen  
excreted in  
urine per 24 hrs.,  
in gm.

Gm. NaCl received  
per 24 hrs.

Chloride (as NaCl)  
in urine per 24 hrs.  
in gm.



Borst: Chronic Renal Insufficiency.





sulphate per cc of blood. The activity could be demonstrated even after storage for 8 days at  $+2-4^{\circ}$  C. Inactivation occurred at pH below 5.8. The enzyme is found in the blood plasma.

The widespread clinical use of the belladonna alkaloids and their substitutes in connexion to the different tolerance of human beings against these substances arises the question, whether human blood contains any atropinesterase activity primarily or if a such factor can be acquired in some way. Ikonen and Kusnetz-kowa in 1927 claimed to have demonstrated a principle in human blood, capable of »neutralizing» atropine in a fairly high amount. This principle was observed in patients, suffering from hyperfunction of the thyroid. No quantitative figures, however, are given in the report, only the statement, that there was a partly »neutralization» of atropine in the proportion of 1 : 50. As test organ the cat's eye was used.

Thus, the question about the existence of atropinesterase activity in the human blood needs further investigation. It seems especially worth knowing, if atropin-esterase activity could be acquired during certain pathological conditions or if prolonged use of atropine can elicit a specific esterase activity in the blood. For these purposes a series of human blood samples were investigated as follows.

### Experimental.

The blood from 288 different human individuals was examined for atropin-esterase activity. A small amount of serum or plasma was mixed up with some few micrograms of atropine or the methonitrate of scopolamine and immediately injected subcutaneously into white mice, the pupils of which than were measured at regular intervals by means of a preparation microscope, according to the method of Pulewka (1932). Further development of the method and calculations of its accuracy are given by Tønnesen.

The material consists partly of healthy individuals, partly of patients from the medical department of Karolinska sjukhuset, Stockholm. The cases were not selected, but consecutive and the investigated number is considered enough to cover the most important field of internal diseases. In order to get information about the possibility of acquired atropinesterase activity, owing to peroral ingestion of big doses of atropine, a series of atropine-treated cases of cerebral disorders of the parkinsonian type was included. These cases had been treated for months with high doses of atropine, and the investigation was done during a pause in the treatment.

Blood samples for testing mainly were taken from citrate plasma, which was left after the routinary erythrocyte sedimentation test. In a series of normal individuals, samples were withdrawn in glass tubes and the serum used. No difference could be demonstrated between serum and citrate plasma as concerning atropin-esterase activity.

The alkaloids were added in quantities shown by the table. The injected amount of serum or plasma constantly was 0.5 ml and the alkaloid was contained in the

same amount of normal saline. The mice were placed on a small, round, rotating table with a capacity of 8 animals. The measuring of the pupil's diameters by means of the preparation microscope ( $30\times$ ) was made in the light of a 40 watt microscope lamp. The diameters of the pupils were determined at regular intervals of 5 minutes in relation to an ocular scale. On an average, maximal mydriasis occurred within 40 minutes, the pupils then having a diameter exceeding 2 mm. The normal value is 0.2—0.4 mm. The same animal was used several times, but never at shorter intervals than 48 hours. A slight darkening of the iris after several tests had been performed did not essentially interfere with the exactitude of measuring. The main results will be seen from following table:

Diagnosis or groups of diagnosis	Atropine 2.5—3 micrograms				Methonitrate of scopolamine 1 microgram			
	added to serum		added to plasma		added to serum		added to plasma	
	no. of cases	max. mydr. in no.	no. of cases	max. mydr. in no.	no. of cases	max. mydr. in no.	no. of cases	max. mydr. in no.
Normal subjects .....	10	10	19	19	5	5	6	6
Pregnancy .....	2	2	3	3	—	—	3	3
Cardiovascular dis. ....	—	—	55	55	—	—	12	12
Joint and bone dis. ....	—	—	36	36	—	—	5	5
Gastrointestinal dis. ....	—	—	31	31	—	—	11	11
Acute resp. infect. ....	—	—	16	16	—	—	3	3
Thyroid dis. ....	6	6	14	14	—	—	—	—
Diabetes mell. ....	3	3	11	11	—	—	—	—
Hepatic dis. ....	—	—	8	8	—	—	—	—
Hypercholesteremia ....	5	5	6	6	—	—	—	—
Nervous dis. ....	—	—	7	7	—	—	—	—
Anemias .....	—	—	6	6	—	—	—	—
Prolonged atropine treatment	5	5	—	—	—	—	—	—
	31		212		5		40	= 288

### Results.

In none out of 288 cases there was found any appreciable power of destroying atropine (243 cases) or the methonitrate of scopolamine (45 cases) in the proportions of some few micrograms of alkaloid to 0.5 ml of serum or plasma. The cases represent healthy individuals, pregnant women, common groups of internal diseases including thyroid disturbances and a series of cerebral disorders of the parkinsonian typ, treated for long times with massive doses of atropine. Hence it must be considered very unlikely, that human blood contains any genetically determined or acquired appreciable power of destroying atropine or quaternary bases of the atropine group.

### Summary.

No appreciable amount of atropinesterase could be detected in human blood during health, pregnancy, some representative groups of internal disorders or after treatment with massive doses of atropine.

### References.

Bernheim, F. & Bernheim, M.: *J. Pharmacol. Exper. Therap.* 1938, *64*, 209. — Fleischmann, P.: *Arch. exp. Path. Pharmacol.* 1910, *62*, 518. — Glick, D. & Glaubach, S.: *J. Gen. Physiol.* 1941, *25*, 197. — Ikonen, M. & Kusnetzowa, S.: *Zeitschr. ges. exp. Med.* 1927, *57*, 353. — Metzner, R.: *Arch. exp. Path. Pharmacol.* 1912, *68*, 110. — Pulawka, P.: *Arch. exp. Path. Pharmacol.* 1932, *168*, 307. — Sawin, P. & Glick, D.: *Proc. Nat. Acad. Sci.* 1943, *29*, 55. — Tønnesen, M. G.: *Studier over nogle mydriatisk virksomme stoffer*, Copenhagen 1947. Munksgaard. — Willberg, M.: *Biochem. Zeitschr.* 1914, *66*, 389.

---



## Quelques considérations sur la lévocardie et présentation de 2 cas personnels.<sup>1</sup>

Par

E. DONZELOT, AM. EMAM-ZADE, R. HEIM de BALSAC & C. METIANU.

(Ce travail est parvenu à la rédaction le 7 janvier 1949.)

Les cardiopathies congénitales les plus complexes sont actuellement diagnostiquées, durant la vie, avec une certaine précision, grâce aux progrès de nos moyens d'investigations, parmi lesquels l'angiocardiographie, quoique dernière venue, prend une place chaque jour plus importante.

Les anomalies architecturales qui compliquent d'une façon quasi constante les vices de position du cœur sont de toutes les malformations cardiaques celles qui posent les problèmes les plus délicats. Ce sont aussi celles qui bénéficient le plus des récentes techniques d'examens.

La lévocardie au cours d'un situs inversus total occupe une place tout à fait spéciale parmi les anomalies congénitales de position du cœur. Cette anomalie pose des problèmes embryologiques des plus intéressants, mais son extrême rareté explique la pauvreté de la littérature à son sujet. En effet le nombre des cas publiés n'excède guère la vingtaine, et la plupart de ces relations ne sont qu'anatomiques.

Sur les 329 cardiopathies congénitales que nous venons d'examiner depuis un an dans notre Centre nous avons observé 15 cas d'anomalies de position du cœur parmi lesquels deux lévocardies.<sup>2</sup> Nous croyons ces cas intéressants, car le diagnostic en a été posé durant la vie et l'angiocardiographie a précisé les malformations surajoutées permettant d'envisager dans le 1<sup>er</sup> cas une intervention chirurgicale. En rapportant ces cas, nous rappelons quelques éléments essentiels concernant la lévocardie.

<sup>1</sup> Travail du Centre des Enfants Bleus de l'Hôpital Broussais (Clinique Cardiologique de la Faculté de Médecine de Paris) Pr E. Donzelot et collaborateurs: Drs A. Pithon, R. Heim de Balsac, A.M. Emam-Zade, J. E. Escalle, M. Durand et C. Metianu. Service de Chirurgie Pr d'Allaines et collaborateurs: Drs G. Dubost, A. Toupet, N. du Bouchet, J. Le Brigand. Service Central d'Electroradiologie: Drs Foubert et collaborateur: Dr Antoine. Ont également participé aux travaux du Centre: Drs Dessertenne, S. Collado, Madera, M. Kolosy, Guery & Passelecq.

<sup>2</sup> Depuis la rédaction de ce travail nous avons examiné, avec le Docteur M. Durand, 252 nouveaux cas de cardiopathie congénitale parmi lesquels nous avons repéré 7 anomalies de position du cœur, dont une lévocardie.

Les premiers cas publiés de lévocardie paraissent être ceux de Gruber (1865) et Hickman (1869). Puis viennent les observations de Griffith et Wardrop (1897), Lochte (1898), Mc Crae (1905), Muller et Herrmann, Royer et Wilson (1908), Keth et Mc Donnel (1921), Shaw et Blake (1924) et Millier (1925). Ces 10 cas sont les seuls mentionnés par Lichtmann (1931) et Maud Abbott (1936).

Depuis cette date nous n'avons trouvé que la mention de 3 cas par H. Taussig dans son livre sur les cardiopathies congénitales (1947) et de deux cas de Forgacs (1947); mais nos recherches bibliographiques sont sans doute incomplètes du fait des circonstances de ces dernières années.

Par *lévocardie* il faut comprendre la situation congénitale du cœur à gauche, avec pointe vers la gauche au cours d'une hétérotaxie totale. Cette affection est ainsi au situs inversus, ce que la dextrocardie isolée est au sujet normal.

Le processus embryogénétique de la lévocardie doit être au cours d'une hétérotaxie l'homologue de celui d'une dextrocardie isolée chez un sujet normal.

La transposition de tous les organes d'un situs inversus se produit dans les premiers stades de la vie embryonnaire. Dans la lévocardie le développement du cœur en situation gauche survient un peu plus tard, mais toujours avant la sixième semaine, la forme avec inversion des cavités étant plus précoce que celle sans inversion. Ces deux bouleversements consécutifs dans le développement du cœur expliquent la constance d'anomalies surajoutées (cavitaires, septales et vasculaires) particulièrement importantes et nombreuses.

Les anomalies de position du cœur (lévocardie) et les malformations surajoutées peuvent relever d'un même facteur causal ou résulter de processus tératologiques indépendants mais survenant simultanément.

Anatomiquement les lévocardies au cours d'un situs inversus peuvent se présenter avec ou sans inversion des cavités. Dans chacune de ces catégories existe une forme idéale strictement symétrique ou purement en miroir et une forme modifiée (non strictement symétrique). Toutes ces formes peuvent être compliquées ou non compliquées. La classification des lévocardies se présente donc ainsi:

Lévocardie	$\left\{ \begin{array}{l} \text{sans inversion des cavités} \\ \text{avec inversion des cavités} \end{array} \right.$	$\left\{ \begin{array}{l} \text{Forme idéale} \\ \text{Forme modifiée} \\ \text{Forme idéale} \\ \text{Forme modifiée} \end{array} \right.$	$\left. \begin{array}{l} \\ \\ \\ \end{array} \right\} \begin{array}{l} \text{non compliquées ou} \\ \text{compliquées} \end{array}$

Cette classification est théorique; seules des formes modifiées et compliquées ont été publiées jusqu'ici.

Notons que les lévocardies, comme toutes les cardiopathies congénitales, peuvent être compliquées d'une lésion acquise.

Cliniquement la lévocardie par elle-même ne présente aucune symptomatologie cardiaque, parce que les bruits du cœur sont normalement situés. C'est l'existence d'un cœur en situation normale gauche et d'une hétérotaxie qui, cliniquement et radiologiquement, caractérisent une lévocardie.

Tous les symptômes subjectifs et objectifs observés au cours des lévocardies appartiennent aux malformations cardio-vasculaires congénitales surajoutées qui sont constantes et éventuellement aux cardiopathies acquises.

Jusqu'ici le diagnostic précis de ces malformations surajoutées n'a posé qu'à l'autopsie; in vivo, de telles précisions sont particulièrement délicates.

Sans négliger l'électrocardiographie ni les épreuves biologiques, c'est l'angio-cardiographie qui nous apportera les éléments les plus décisifs. Nos 2 cas en sont un exemple.

*Observation 1: Boud. Nicole, fille, 4 ans.*

Aucuns antécédents familiaux.

Naissance à terme. Au 13<sup>e</sup> jour l'apparition de dyspnée et de cyanose fait découvrir la cardiopathie et nécessite déjà l'oxygénothérapie. Premiers pas à 3 ans 1/2; depuis cette époque la cyanose et la dyspnée vont en s'accroissant.

*Actuellement:* L'activité physique est réduite (l'enfant ne peut marcher que 300 mètres et monter à peine un étage). Développement chétif (14 kgs), dyspnée, vomissements fréquents, pas d'accroupissement, facies adénoïdien avec rhinite ozéneuse. Cyanose et hippocratisme intenses.

Au 3<sup>e</sup> espace intercostal droit et derrière le sternum claquement du 2<sup>e</sup> bruit et souffle continu à renforcement systolique se propageant surtout vers la clavicule droite et le dos. Au 4<sup>e</sup> espace intercostal gauche éclat du 1<sup>er</sup> bruit et petit souffle systolique irradiant en particulier vers l'aisselle et le dos. Quelques ronchus en avant et surtout du côté gauche du thorax. Pouls: 100 petit et égal aux quatre membres. T. A.: 120/60 (aux 2 bras), matité hépatique à gauche, sonorité gastrique à droite. Polyglobulie: 8,690,000. Vitesse de sédimentation et taux d'hématocrite en rapport, légère augmentation des leucocytes sans polynucléose. Vitesse circulatoire: 4" à l'éther avec effet positif. Température normale. E. C. G.: Rythme sinusal. Déviation de l'axe à droite (autour de + 130°). Légère prédominance (axe de R et de S à droite). P positif et normal dans les trois dérivations. Sens dextrogyre de la boucle vectorielle.

*Radio:* En frontale, hétérotaxie abdominale totale, foie à gauche, estomac à droite, hémidiaphragme droit normalement surélevé. Cœur situé à gauche avec pédicule à droite; il est couché. Son bord droit est saillant; la pointe peu volumineuse est acumminée et relevée. La base du bord gauche est rectiligne jusqu'au bord droit du rachis où se trouve la totalité du pédicule. Œsophage dévié vers la gauche. Image de la veine cave supérieure sur le bord pédiculaire droit. Artères pulmonaires peu volumineuses, non battantes, léger flou hilare.

En O. A. D., l'œsophage et la trachée ne sont pas déviés, l'aorte n'est pas rétro-œsophagienne, l'espace rétro-cardiaque est presque normal.

En O. A. G., tout le pédicule file vers l'avant, l'aorte descendante se discerne en avant du rachis.

En T. G., rien de particulier à signaler.

*Opacification* (Position frontale antéro-postérieure): Sur le premier cliché à la première seconde, la veine cave supérieure forme la totalité du bord droit du pédicule circonscrivant l'arc aortique à droite. La veine cave inférieure est également injectée. L'oreillette droite occupe le secteur droit du cœur et est normale comme aspect et situation, elle communique largement avec le ventricule droit qui, bien injecté, atteint la pointe; l'infundibulum très incliné est peu volumineux. Au-dessus de lui s'injecte un tronc vasculaire; à son origine des images sigmoïdiennes se discernent. Par sa direction de gauche à droite et son calibre régulier et normal, il ne peut être que le tronc de l'aorte ascendante. L'hémicercle est à droite et la descendante sur le bord droit du rachis. Le tronc de la pulmonaire ne se discerne pas, mais sa bifurcation forme une ombre nummulaire médio-pédiculaire. Une seconde après (sur le 2<sup>e</sup> cliché) les cavités droites se libèrent; l'infundibulum plus net paraît sténosé. L'aorte visible dans sa totalité ainsi que ses branches cervicale et abdominale présente une descendante sinueuse qui du bord droit passe sur le bord gauche du rachis. La bifurcation pulmonaire est toujours visible, la pulmonaire gauche est totalement injectée, formant la majeure partie de l'arc moyen. La pulmonaire droite est à peine visible. Sur les clichés 3, 4 et 5 (3<sup>e</sup>, 4<sup>e</sup> et 5<sup>e</sup> seconde après l'injection) les cavités droites et l'aorte se libèrent progressivement, toute la substance opacifiante est dans les champs pulmonaires, surtout à gauche, très peu à droite, où les ar-

borisations artérielles, particulièrement nettes, présentent un aspect en lacis et même piqueté très instructif. Les clichés 5 et 6 (5<sup>e</sup> et 6<sup>e</sup> seconde) montrent un retour dans les veines pulmonaires particulièrement net surtout du côté gauche, l'oreillette gauche étant en situation normale.

### Commentaires.

- 1) Cette hétérotaxie présente une particularité: une lévocardie.
- 2) Cliniquement la cyanose précoce et intense, le souffle continu, le souffle systolique et le claquement du 2<sup>e</sup> bruit caractérisent des malformations surajoutées.
- 3) L'effet très positif de l'épreuve à l'éther implique un shunt veino-artériel important.
- 4) L'électrocardiogramme traduit une modification des cavités droites, comme s'il s'agissait d'un cœur en position normale chez un sujet sans situs inversus.
- 5) L'étude radiologique confirme la lévocardie et montre une silhouette cardiaque peu volumineuse, à pointe acumulée, avec arc aortique à droite et arc moyen dégagé, c'est-à-dire une des modalités les plus caractéristiques de la tétralogie de Fallot. Cette constatation cadre avec les données cliniques qui décèlent en plus l'existence d'un canal artériel.
- 6) L'opacification montre des cavités droites en situation normales avec injection précoce de l'aorte. L'origine de ce vaisseau est donc dextroposée et se trouve à cheval sur une communication interventriculaire haute. L'infundibulum pulmonaire n'a pas une forme en champignon comme chez le sujet normal; il doit être fortement sténosé, il alimente une aorte volumineuse et un arbre artériel pulmonaire dont le tronc n'est pas visible. Ce tronc est donc très réduit ou atrésié. Enfin les artères pulmonaires s'injectent après l'aorte (sur les clichés suivants); ce retard s'explique bien par un canal artériel persistant qui, comme nous l'avons vu, se traduit cliniquement par le souffle continu caractéristique; celui-ci siège à droite comme l'arc aortique ce qui est logique. Fait démonstratif, l'artère pulmonaire gauche particulièrement visible ainsi que toutes ses branches s'opacifie presque seule, la droite paraissant de dimensions réduites dans un champ pulmonaire à peine habité. Très probablement le canal artériel s'insère comme il est habituel sur la naissance de l'artère pulmonaire gauche qui est de ce fait amplement irriguée.
- 7) L'aspect des champs pulmonaires surtout le gauche sur les clichés 3, 4 et 5 est très particulier; la netteté des arborisations artérielles pulmonaires s'efface rapidement. L'image est celle d'un lacis en réseau, à mailles de plus en plus floues et même presque piquetée. Cet aspect est exactement celui du champ pulmonaire de certains enfants cyanosés au stade de mauvaise tolérance de leur cardiopathie. Nous pensons avoir ainsi expérimentalement établi que ces images si spéciales de flou hilaire ou hilo-pulmonaire sont bien d'origine vasculaire et non parenchymateuse.
- 8) Le passage de la substance opacifiante dans les veines pulmonaires apparaît sur la cinquième cliché (5<sup>e</sup> seconde) et gagne l'oreillette gauche sur le 6<sup>e</sup> cliché. La topographie de ces organes, d'ailleurs normale, est bien précisée.

Un enregistrement du phénomène plus étendu dans le temps aurait montré l'opacification du ventricule gauche et la réinjection de l'aorte, mais la dilution progressive de la substance opaque n'aurait donné que des images moins contrastées.

### Diagnostic.

L'ensemble des investigations implique dans ce cas un diagnostic assez précis: Lévocardie, sténose très serrée ou atrésie pulmonaire, communication inter-ventriculaire haute, aorte à cheval, arc aortique à droite, persistance du canal artériel alimentant surtout l'artère pulmonaire gauche.

### Conclusion.

La vie de cette enfant semble tributaire du bon fonctionnement de son canal artériel, mais l'insuffisance du débit de ce canal est prouvé par l'état précaire de la malade. Une intervention chirurgicale du type Blalock-Taussig est donc indiquée pour améliorer l'alimentation pulmonaire. Il serait logique d'effectuer une anastomose à droite; les dimensions très réduites de l'artère pulmonaire droite permettent de penser qu'une anastomose termino-terminale sera plus profitable. Une anastomose pratiquée à gauche sera sans doute plus facile, mais le clampage de la pulmonaire gauche sera probablement mal supporté par cette enfant dont la circulation pulmonaire droite est si défectueuse. D'autre part elle exposerait à une surcharge circulatoire du poumon gauche.

### Autopsie.

L'opération est décidée, la mort survient sur la table d'opération par arrêt brutal du cœur avant même que l'artère pulmonaire droite ait été abordée. L'autopsie montre un ventricule unique avec sur sa paroi gauche, particulièrement épaisse, une cavité rudimentaire. L'orifice auriculo-ventriculaire unique draine le sang des deux oreillettes; ces dernières, recevant normalement le sang veineux et artériel, présentent une communication large occupant les 2/3 de la partie inférieure du septum. L'orifice aortique à trois valvules se trouve en avant de l'orifice auriculo-ventriculaire. L'aorte ascendante est particulièrement large, l'arc aortique est à droite. De la concavité de cet arc part un canal artériel du diamètre d'un crayon et atteignant l'origine de l'artère pulmonaire gauche dont le diamètre est le double de celui du canal artériel et le triple de celui de l'artère pulmonaire droite. Le tronc de l'artère pulmonaire est hypoplasie; son orifice ventriculaire à gauche de celui de l'aorte est obstrué et atrésié:

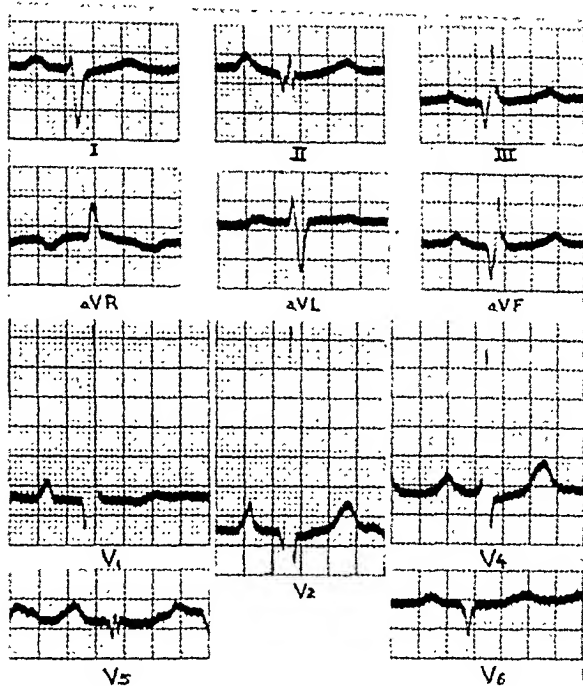
— le poumon gauche possède 3 lobes et celui du côté droit n'en possède que deux

— le foie est très volumineux, son lobe principal et la vésicule biliaire se trouvent à gauche

— l'estomac est à droite

— la rate rudimentaire se trouve à droite

— les reins sont normaux.



Obs. I, fig. 8.

*Observation 2. — Cris ... Annie, fille, 3 ans*

Au 15<sup>e</sup> jour de la vie l'apparition d'une cyanose légère fait découvrir la cardiopathie. Dyspnée, accroupissement et lipothymies. Taille 88 cm. Poids 12 kgs. Cyanose très modérée sans hippocratisme.

Choc apexien perçu sous le mamelon gauche. Souffle systolique sans frémissement au 3<sup>e</sup> EIG près du sternum se propageant dans toutes les directions, surtout sous la clavicule gauche. Pouls régulier à 90. T. A. 110/90. Indice oscillométrique: 2. Globules rouges: 4,910,000. Vitesse circulatoire: 7" à l'éther avec effect positif. Matité hépatique à gauche, sonorité gastrique à droite.

*E. C. G.* — Déviation de l'axe à droite (+ 140°) avec prédominance.

*Radio.* — Cœur augmenté de volume et transversal; bord droit à peine convexe, pointe relevée, légèrement acumminée, base du bord gauche rectiligne. Pédicule court, hémicercle aortique en place, confirmé par l'encoche œsophagienne opacifiée. Les artères pulmonaires et leurs branches, de volume presque normal, sont peu battantes, la gauche cachée par l'ombre cardiaque, la droite recouverte d'un léger flou biliaire. Transparence pulmonaire satisfaisante à distance. La clarté de la poche à air gastrique se trouve à droite et l'ombre hépatique à gauche.

En O. A. D. la masse cardiaque atteint la paroi thoracique; l'arc moyen paraît à peine concave. L'espace rétro-cardiaque s'éclaire.

En O. A. G. la masse cardiaque s'efface difficilement, le bord antérieur du cœur est court presque normal, la boucle aortique est assez ample, la fenêtre vasculaire est normale, l'artère pulmonaire gauche se discerne à peine.

En T. G. l'espace rétro-cardiaque est large; le cœur colle contre la paroi antérieure.

*Angiocardiographie.* — Faite en collaboration avec le Dr Durand, montre sur le 1<sup>er</sup> cliché (2" après l'injection de la substance opacifiante) des images peu nettes; on discerne toutefois une veine cave supérieure volumineuse et une oreillette droite en place.

L'opacification simultanée: 1) de l'artère pulmonaire et de ses branches qui sont assez accusées; 2) de l'aorte thoracique et de ses collatérales, témoigne une communication interventriculaire et d'une aorte à cheval.

### Commentaires.

L'apparition précoce de la cyanose, la dyspnée, l'accroupissement, les crises lipothymiques, le souffle systolique, la légère polyglobulie, la positivité de l'épreuve de l'éther et la déviation à droite de l'axe électrique, indiquent la présence d'une cardiopathie congénitale cyanogène et amènent la pensée à priori vers une tétralogie de Fallot, mais l'aspect radiologique du cœur, du pédicule et des branches artérielles pulmonaires prêt à discussion.

L'angiocardigraphie montre d'une façon certaine l'injection simultanée de l'aorte et de l'artère pulmonaire; le volume de celle-ci ainsi que celui de ses branches est à peu près normal.

Il s'agit donc d'une lévocardie compliquée de communication interventriculaire haute et de dextroposition de l'origine aortique sans ou avec sténose pulmonaire très légère.

### Summary.

The authors reported about 2 cases of complicated levocardia with total situs inversus observed at the Centre for Blue Children in the Broussais Hospital (Paris), in a total amount of 329 cases of congenital heart disease, 14 of which with abnormal position of the heart.

After a short historical and clinical review of the question (of the matter) they mentioned the observation of 2 cases, diagnosed by angiocardigraphy during life, and in one case, affirmed by autopsy.

In the first case investigation allowed clinical diagnosis of levocardia with situs inversus, complicated by extremely tight pulmonary stenosis or pulmonary atresia, interventricular communication, horseshoe aorta, aortic arch to the right side, hypertrophy of the right ventricle and ductus arteriosus supplying specially the left pulmonary artery.

The autopsy showed one single ventricle, one single auriculoventricular orifice and one large interauricular communication, occupying two thirds of the inferior part of the septum. The aorta is large. There is a persistent arterial canal.

The pulmonary truncus is hypoplastic.

Its two branches, specially the right, are small. The abdominal organs and the lungs are inverted.

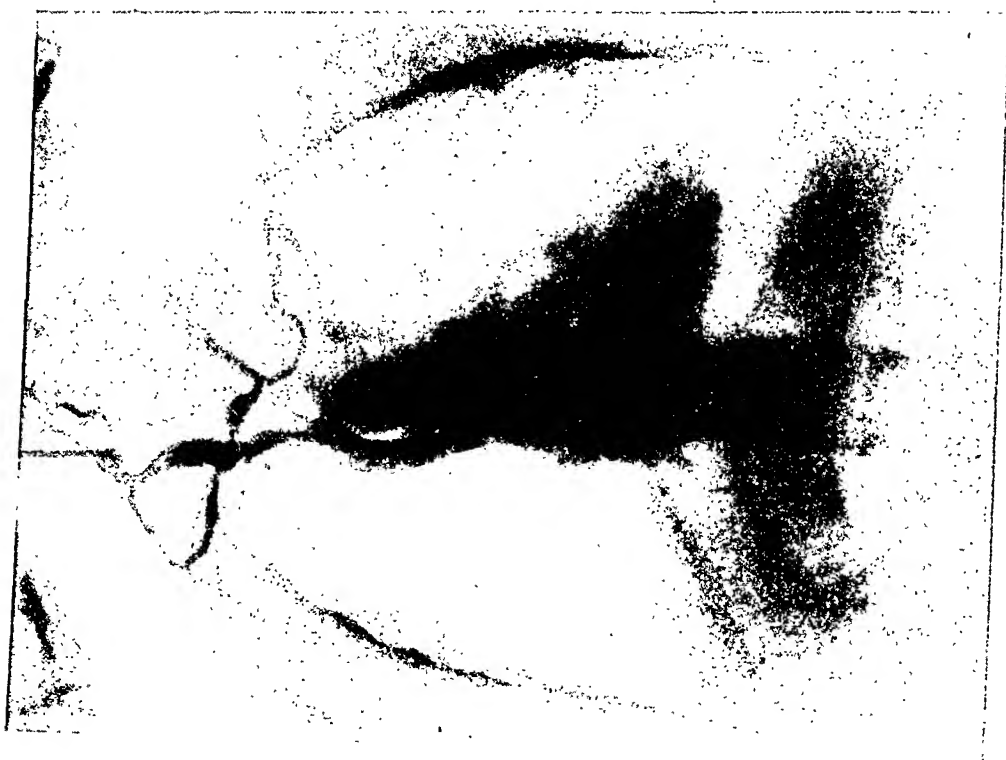
In this second case there exists a levocardia with a situs inversus, complicated by a high interventricular communication, dextroposition of the aortic orifice without or with a very slight pulmonary stenosis.

## Bibliographie.

Abbott, M. E.: Atlas of congenital heart disease. Am. H. Assoc. New York 1936. — De F. Bauer, D. & Astbury, E. C.: Congenital cardiac disease. Bibliography of the 1,000 cases analyzed in Maude Abbott's Atlas Am. H. J. 27: 688, 1944. — Crae, Mc J.: A case of congenital atresia of pulmonary artery with transposition of viscera. A second case of transposition. J. Anat. Physiol. 11: 28, 1905—1906, cited by Abbott. — Forgacs, P.: Congénital heart disease with isolated inversion of the abdominal viscera. British Heart Journal 9: 27, 1947. — Griffith, Wardrop: Transposition of the heart. Brit. M. J. 1: 1287, 1897, cited by Foggie. — Gruber, W.: Ueber das Vorkommen eines Mesenterium commune für das Jejunum-Ileum und die grössere Anfangshälfte des Dickdarms seitlichen Transposition der Viscera aller Rumpfhelen. Arch. F. Anat. H. Physiol. 558, 1865. — Hickman: Tr. Path. Soc. London 20: 88, 1869. cité par Laubry & Abbott. — Keth, A. & Mac Donnell, J. J.: Case of transposition of viscera showing a potentially bicameral heart. Proc. Roy. Soc. Med. 14 pts 1—2. Sec. Med. 1—7, 1921. — Lichtmann, S. S.: Isolated congenital dextrocardia; anatomic, clinical, Roentgenologic and electrocardiographic studies of the cases reported in the literature. Arch. Int. Med. 48: 683—866, 1931. — Lochte: Beitrag zur Kenntnis des Situs transversus partialis und der angeborenen Dextrocardie. Beitrag z. Path. Anat. u. z. Allg. Path. 16: 189, 1894, cited by Foggie. — Miller, A. J.: Congenital heart disease with partial situs inversus, absence of inferior vena cava and other anomalies. Am. J. Path. 1: 46, 1925, cited by Sakurai. — Robb, G. & Steinberg, I.: Visualisation of chambers of heart, pulmonary circulation and great blood vessels in man; Summary of method and results. J. A. M. A. 114: 474, 1940. — Royer, B. F. & Wilson, J. D.: Incomplete heterotaxy with unusual heart malformations: Case report. Arch. Pediat. 25: 881, 1908. — Shaw, E. & Blake, H. K.: Transposition of the abdominal viscera: reversal of the heart chambers with left-handed heart. Am. J. Dis. Childr. 28: 204, 1924. — Taussig, H. B.: Congenital malformation of the heart. New York, the Commonwealth Fund 1947.

---





Obs. I, fig. 2.



Obs. I, fig. 1.



Obs. I, fig. 4.



Obs. I, fig. 3.



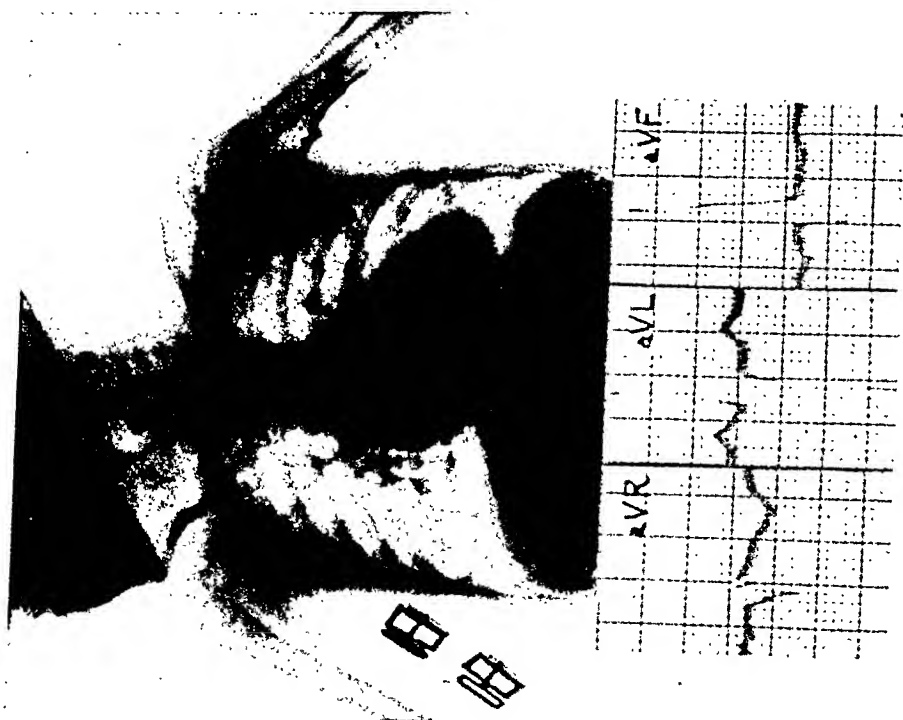
Obs. I, fig. 6.



Obs. I, fig. 5.



Obs. I, fig. 7.



Obs. II, fig. 2.



Obs. II, fig. 1.

From the Orthopaedic Hospital of the Invalid Foundation, Helsingfors. Chief: Professor F. Langenskiöld, and from the IV Medical Clinic of the Helsingfors University, Chief: Professor Bertel von Bonsdorff.

## Looser-Milkman's Syndrome with Neurofibromatosis Recklinghausen and General Decalcification of the Skeleton.

By

C. A. HERNBERG and WALTER EDGREN.<sup>1</sup>

(Submitted for publication January 26, 1949.)

Insidious spontaneous fractures were observed as early as by von Recklinghausen. But not until 1920 were they studied more closely by Looser in his investigations of late rickets and osteomalacia. He found that in these diseases changes sometimes occurred which on superficial examination seemed to be fractures but in reality were decalcified, so-called transformation zones (Umbauzonen) in the bone structure and were revealed by X-ray photography as transparent bands.

Milkman, in 1934, described a condition with multiple, doublesided Looser's zones approximately symmetrically distributed as a specific, idiopathic disease. The onset of the disease is insidious and it develops in periods of varying activity. The first symptom is usually low back pain, causing the patient to waddle. Later pain and tenderness to pressure appear also in other parts of the skeleton. Classical symptoms of fractures are absent. In advanced cases the body length may be considerably reduced owing to skeletal deformations.

On the X-ray photograph the bones seem to be crossed by clear bands from one mm to one cm wide, as if there the bone structure had been removed. Otherwise the bone has a fairly normal appearance.

At the beginning of the process the cortex shows a small, round or irregularly punctuated, decalcified area which gradually spreads and encircles the bone.

The periosteum is uninjured and the outline of the bone at first remains unbroken. Only at an advanced stage and in places where the strain has been great do dislocations and deformations appear.

Signs of spontaneous regression are few and are indicated in the X-ray by two denser bands, one on each side of the transparent zone. The fragment ends remain

<sup>1</sup> Fredsgatan 7, Helsingfors.

sharp. As a rule an insignificant swelling of the periosteum appears though it does not become calcified.

Histologically the bone within the zone is transformed from the original lamellar into trabecular bone or it consists of uncalcified osteoid tissue (Wettstein).

Looser's zones are considered the results of physiological overloading of a bone already having weak resistance. They preferably occur in parts where the strain is great. In the first place the pelvis and the necks of the femora and scapulae are affected; but the zones may occur in any part of the skeleton except the upper jaw (Wettstein). The zones appearing in the calvarium of the skull are said to be round. In other flat bones they proceed in zigzag fashion from the margin towards the centre of the bone. A certain degree of osteoporosis belongs to the clinical picture.

About 60 cases of insidious, symmetrical pseudofractures have been published. In a critical study of the literature Herold has classified them as follows: 1. Cases with unfavourable prognosis: «Milkman's disease», renal osteopathia, cystine disease. 2. Cases with favourable prognosis: hunger osteomalacia, convent osteomalacia, sprue osteomalacia, Basedow osteomalacia. 3. Cases with uncertain prognosis: certain cases of Basedow osteomalacia, osteomalacia in hypophyseal, parathyroidal or ovarian dysfunction.

The prognosis is dependent on the possibility of treating the underlying disease. The existence of a specific, idiopathic «Milkman's disease» is doubted by most authors. They consider the condition a syndrome, which may appear in connection with several different skeletal diseases but especially in osteomalacia. Milkman's own case was, as noted by Herold and others, not sufficiently studied in that respect.

The blood chemistry in Milkman's syndrome is due to the underlying disease. A low phosphorus value combined with a high phosphatase value of the blood often indicates osteomalacia.

The disease affects women mostly.

Some cases have been examined post mortem but no other etiology has been discovered than the fundamental diseases mentioned above.

### Report of a Case.

V. L., 39 years old, carpenter's wife. Heredity: nothing noteworthy. Apart from having suffered from migraine, she has been on the whole healthy. She has lived in the country on vitamin rich food. Prior to the present illness her work was mostly in the open air. At the age of 32 she began to feel a pain in the sacral region and in the feet, especially when walking. When she was resting the pain ceased. At that time also multiple, soft, bean-sized nodes appeared in various parts of the body simultaneously with a number of small moles. During recent years some ten or more nodes have been removed by various colleagues, who considered them neurofibromas.

During the last two years the patient has been incapable of rising from a sitting position without help. A couple of months ago considerable tenderness over the ribs and the sternum appeared. Her height has decreased by at least 10 cm during the years of her illness.

Menarche at the age of 18. No pregnancies. During the last year haemorrhage ex utero every second week.

The patient was admitted to the Hospital of the Invalid Foundation in Hel-

singfors on Oct. 29, 1947, and was transferred to the IV Medical Clinic (Maria Hospital) on Nov. 14, 1947. — General condition good. Weight 45.5 kg, height 147 cm (Fig. 1.) Gl. thyr., internal organs and urine normal. Gynecological finding 0. Slight thoracic kyphosis and lumbar lordosis. The rotation of the right hip joint slightly restricted, otherwise complete motility of all joints. The patient admits tenderness over the ribs and the sternum. Her gait is laborious and painful, and accompanied by rocking movements of the pelvis. On the body and the arms are numerous naevi pigmentosi as well as about fifteen neurofibromas the size of a finger's end (histologically established by I. Wallgren). Several scars from previous extirpations of neurofibromas. Nothing special in other organs.



Fig. 1.

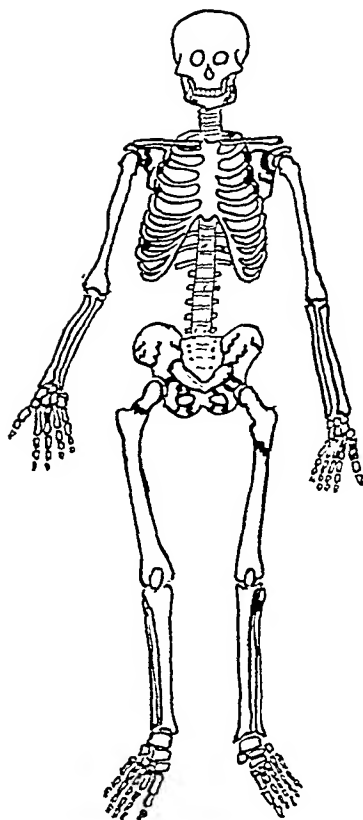


Fig. 2.

### X-Ray Findings.

The bone tissue is characterized by a remarkable poor-ness in calcium and the compacta is relatively thin. In 41 places typical Looser's zones, their distribution shown in Fig. 2.

The width of the zones varies from 1 to 4 mm, and several of them touch denser border areas. Others show no signs of regressive processes.

Pelvis (Fig. 3): Looser's zones found in 16 places. Rami ossium ischii et pubis disconnected in 10 places, acetabula deformed. In the alae ossium ilei 6 zones run zigzag from the margin towards the centre. The pelvis as a whole is somewhat compressed from the sides and the inlet is triangular.

Lower limbs: The right collum femoris disconnected by a Looser's zone causing varus position. The left femur interrupted somewhat distally from the trochanters but not dislocated. The right fibula interrupted immediately below the collum. Metatarsalia II, III, IV and V of both feet show typical Looser's zones. Metatarsalia II and III further disconnected at the collum and the hallux in its outer phalanx.

Columna vertebralis: Looser's zones in arcus vertebrae cervicalis IV and lumbalis II and III. The spine shows an increased thoracic kyphosis and marked lumbar lordosis. The structure of the vertebrae is indistinct. The height of the vertebrae is slightly reduced and shows a tendency towards biconcavity in the thoracic region.

Thorax: Transversal pseudofractures in the left costae I—IV and the right II—IV and VII.

Skull: Theca cranii thin, bone structure diffuse. A few round, pea-sized, partly confluent clarifications in the calvarium and the mandibulae. The sella turcica normal in size, dorsum sellae vaguely defined and poor in calcium.

Upper limbs: Symmetrical clear bands in the necks of the scapulae. In the right scapula complete disconnection of the collum. In the left scapula a zone penetrating a few cm from the margo lateralis towards the centre. The hand shows juxta-articular reduction of the calcium content and an



indistinct bone structure. At the base of the left metacarpale I a recent zone extending from the volar outline of the bone half-way through it. Healed pseudofractures in the left os metacarpale II and in the outer phalanx of the right thumb. In the distal part of the right metacarpale I a cystic, transparent area.

For histological examination a small portion is removed from the left fibula near the Looser's zone. Microscopic examination (I. Wallgren) shows that the zone is a mesh-work of decalcified, osteoid tissue and connective tissue containing a few solitary osteophytes of lacunar bone. The periosteum slightly swollen though not distinctly defined against the zone tissue.

The blood picture and the bone marrow picture in every respect normal. At the sternal puncture the trocar pierces the cortex as easily as a piece of paper.



Fig. 3.

Sedimentation rate 12. Urine and liquor normal. WR and Kahn negative.

Serum cholesterol 230 mg per cent, serum calcium 9.8 to 11.2 mg per cent (several controls). Serum phosphorus 2.3 mg per cent, serum phosphatase 3 BE. Serum protein 6.7 per cent, albumen 3.9 per cent, globulin 2.8 per cent.

The mean output of calcium in the urine during 4 days was 69.2 mg a day, or slightly less than in a normal control.

Thus, apart from the fairly low phosphorus value, the blood chemistry did not differ very much from the normal, and did not definitely support the assumption of osteomalacia. A certain reservation is indicated as regards the phosphatase value which is not absolutely reliable.

As the pictures of the skeleton showed a marked general decalcification intensive treatment was started with calcium lacticum per os and vitamin D intramuscularly. From early December 1947 to early March 1948, the patient received a total of about 11 million i. u. of vitamin D and about 1/2 kg calcium per os. Yet in July 1948 no subjective improvement was noted. Nor had an X-ray examination in May revealed any objective improvement. The patient then moved to the northern part of Finland and no X-ray examination could be made before the 11th Nov. 1948, and then in a different hospital. Since August, however, her condition had steadily improved so that she was able to walk



Fig. 4. X-ray 16. 12. 1947.



Fig. 5. X-ray 11. 11. 1948. Note the beginning calcification of the zone in the rib.

without difficulty, get up from a sitting position without support and carry out her household duties. In her own opinion she was cured. The X-ray photographs (Fig. 4 and 5) also showed a distinct recalcification of the skeleton and a partial consolidation of several transformation zones.

### Discussion.

Our patient, the wife of a tradesman in good social conditions, begins at the age of 32 years to suffer, without apparent cause, from low back pain and pain in the legs. During the following 7 years the pain gradually becomes more acute, especially when she is walking, but disappears when she is resting. Simultaneously she develops neurofibromatosis Recklinghausen. An X-ray examination reveals some 40 pseudofractures or Looser's zones, situated almost symmetrically on both sides. The clinical development, the histological picture and the X-ray findings are uniformly typical of Milkman's syndrome. The bone substance is remarkably poor in calcium in the unaffected parts of the skeleton. There is a thinning of the cortex established roentgenologically as well as by sternal puncture. Although the blood chemistry is normal, the roentgen examination favours the opinion that the patient suffers from a general bone disease. Intensive vitamin D treatment for 3 months causes no improvement but 5 months later the pain gradually disappears and an X-ray examination 11 months after the beginning of the treatment reveals a distinct increase in the skeletal calcium and a consolidation of several transformation zones.

The classification of the skeletal defect, which in our case gave rise to Milkman's syndrome, offers certain difficulties. The exclusion of both osteitis fibrosa generalisata v. Recklinghausen and osteopsathyrosis appears to be justified. Among other things, the blood calcium ratio in the former disease is high, the phosphorus ratio low and the urine calcium excretion high. Yet in our case the blood chemistry and the output of urine calcium were normal. Again, the osteopsathyrosis is definitively a childrens disease. The fractures in osteopsathyrosis are real fractures and are preceded by a certain, if slight, trauma. Our patient did not show real fractures but only broken continuity in the calcium-containing part of the bone substance, without noteworthy dislocation of the fragments.

We were unable to establish any disease of the kidneys or any distinct endocrine disturbance in our patient. The cystine diseases as affecting mainly children was not considered.

Osteomalacia is held to be the commonest fundamental disease in Milkman's syndrome (Herold, Mondor, Leger, Uehlinger, Wettstein). Well known characteristics of osteomalacia are responsiveness to vitamin D therapy and a high blood phosphatase value. Although the phosphatase values of our laboratory are not absolutely reliable, those obtained were so low that they could not be used for the diagnosis osteomalacia. The low phosphorus value may perhaps suggest osteomalacia. Actually the vitamin D treatment led to a favourable result but only after very large doses and much later than has been observed by other authors in typical osteomalacia.

However, MacCance has published a case of D vitamin resistant osteomalacia with Milkman's syndrome, which healed only after about 23 million i. u. of vitamin D. Albright has personally reported to us his knowledge of two more similar cases.

An interesting feature in our case is the combination of neurofibromatosis and osteoporosis. The skeletal changes in neurofibromatosis are well known and have been described by a great number of authors (Armelin, Hagelstam, Nørgaard, Stalman, Thannhauser and others). The local changes in the bone due to the proximity of the neurofibroma are of minor interest. But in neurofibromatosis there are also general changes of the skeleton considered as parallel to the neurofibromatosis and like it due to embryogenous disturbances. The skeletal changes may consist in unilateral gigantism or gracility of the skeleton, or in gracility of the spine alone, with kyphoscoliosis as a result. In earlier literature one may find osteomalacia mentioned in connection with neurofibromatosis, but this is probably due to defective terminology and refers only to osteoporosis in general and not to D vitamin susceptible osteomalacia in the modern sense. However, Hagelstam, in a study of the literature, found 3 cases of real osteomalacia in connection with neurofibromatosis. Irrespective of the classification of these conditions, it can be stated that general skeletal changes with extensive decalcification of the entire skeleton may occur also in neurofibromatosis. Nørgaard's case shows that a Looser's zone may develop in neurofibromatosis with skeletal changes.

No cases of combined neurofibromatosis and Milkman's syndrome seem to have been published. The exact nature of the skeletal disturbance in our case is impossible to ascertain. In view of the rarity of both neurofibromatosis and Milkman's syndrome a simultaneous occurrence of the two conditions can hardly be considered a co-incidence. If the case is regarded as osteomalacia it has *ex iuvantibus* to be referred to the vitamin D resistant type described by MacCance. Exogenous osteomalacia can almost certainly be excluded. No other cases of osteomalacia were found in the patient's family or the neighbourhood. Previous to her illness she had spent much time in the open air and her diet was satisfactory. Nor did she show symptoms of sprue, Basedow's disease, affections of the kidneys or other conditions favourable to the development of osteomalacia.

### Summary.

A carpenter's wife, in good social conditions, begins at the age of 32 to suffer from increasing low back pain when walking. Simultaneously multiple neurofibromas and naevi pigmentosi appear. Her invalidity increases so that she is unable to rise from a sitting position without help, and she has to use crutches. When she is 39 years an X-ray examination reveals a typical Milkman's syndrome with some forty, almost symmetrical, pseudofractures (Looser's zones) preferably localized to the pelvis, the shoulder girdles, the necks of the femora and the metatarsalia.

The skeleton is markedly decalcified. Blood chemistry normal with the excep-

tion of a relatively low serum phosphorus value. Following an intensive vitamin D treatment a certain improvement takes place, but not before 8 months after the beginning of the treatment.

The general changes of the bone substance are assumed to be the direct condition for the development of Milkman's syndrome in the patient.

The inferiority of the bone substance may be thought to have developed as a parallel phenomenon with the neurofibromatosis or possibly because of raised resistance to vitamin D.

#### References.

- Albright, F.: *Medicine*, 25. 399. 1946.— Albright, F.: personal communication 1948. — Armelin, G.: *Les dystrophies osseux de la neurofibromatose*. Thèse. Paris 1932. — Brunner, W.: *Acta chir. sc.* 199. 429. 1940. — Caldwell, G. and Broderick, T. F.: *Ann. Int. Med.* 27. 114. 1947. — Cavallero, C.: *L'ospedale Maggiore*, 36. 1948. — Hagelstam, L.: *Acta chir. sc.* 93. 169. 1946. — Herold, J.: *Symmetrische schleichende Spontanfrakturen: Milkman'sche Krankheit und Milkman'sches Syndrom*. Basel. 1944. — Lepennetier, T. et al.: *J. de radiol. et d'électrol.* 1944—45. — Looser, E.: *Deutsch. Ztschr. f. Chirurgie*, 152. 210. 1920. — Milkman, L.: *Am. J. of Radiology* 32. 632. 1934. — MacCance, R. A.: *Qv. J. Med.* 61. 33. 1947. — Mondor, H. and Leger, L.: *J. de Chirurgie (Fr)* 63. 86. 1947. — Norgaard, T.: *Acta Radiol.* 18. 460. 1937. — Stalman, A.: *Virchows Arch. f. Path. u. Anat.* 289. 96. 1933. — Thannhauser, S. J.: *Medicine* 23. 10. 5. 1944. — Wettstein, P.: *Acta radiol.* 28. 281. 1947.

From the Roentgen Clinic of the State Hospital, Copenhagen.  
(Chief: Prof. P. Flemming Møller, M. D.)

## Combined Kymographic and Electrocardiographic Studies of the Duration of the Presphygmic Period.

By

BRYAN FABRICIUS.<sup>1</sup>

(Submitted for publication January 26, 1949.)

The presphygmic period is the space of the cardiac systole between the closure of the atrio-ventricular valves and the instant when the semilunar valves open and the ejection of the blood begins. Its duration is usually determined by taking cardiograms and pulse curves simultaneously. By this method it was by Robinson & Draper (5) found to be from 0.07 to 0.987 second, by Edens (2) on the average 0.07 second, by Weitz & Graner (8), in studies on rabbits, from 0.045 to 0.085 second, by Blumberger (1) varying from 0.05 to 0.10 second. By Katz (1941) (3) it is stated to be, in the normal subject with a frequency of 78, 0.04 second.

In the following I shall describe a method by which I have been able to determine the duration of the presphygmic period by a combination of electrocardiography and kymography ad modum Stumpf (7) with 36 mm grid diaphragm and falling film, — a method which makes it possible both to obtain lengthy curves rich in details and to get the cardiac movements registered as far as possible corresponding to one single point.

The patient is placed on the roentgen couch, which is sloped at an angle of 70 degrees; in which position he is better able to relax without the position of the heart in the thorax being altered from what it would be if he were standing upright. Under screening, one of the slits of the grid diaphragm is then brought in juxtaposition to the most prominent point of the left ventricular border or — if it is impossible otherwise to get the movements corresponding to the aortic arch registered — close to it. The patient is connected to the cables from a transportable electrocardiograph, the falling-time of the kymograph is calculated to between one and a half and two contractions of the heart, and the recording is then made with the two apparatus simultaneously, the registration with the electrocardiograph being begun before and ended after that of the kymograph.

<sup>1</sup> Vardegade 21, Copenhagen.

During the exposure from the tube there will be thrown into the patient a current with the same frequency of oscillation as that of the alternating current used, — that is 50 per second, and this is transmitted to the electrocardiogram, where the tracing, instead of the usual heavy line, takes the form of a finely serrated, on which the otherwise occurring waves are, however, distinctly seen. As this serrated line commences and stops simultaneously with the exposure from the tube, it is possible on the electrocardiogram exactly to delimit the section corresponding to the kymographic segment; and as there are time-markings both on the electrocardiogram and the kymogram, it is possible to determine the relation between the former

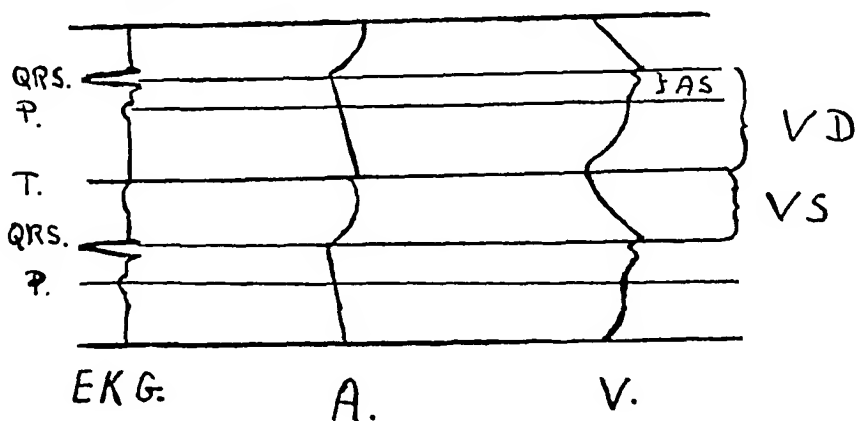


Fig. 1. EKG: Electrocardiogram. A: Marginal curve of aorta. V: Marginal curve of left ventricle. VD: Duration of ventricular diastole. VS: Duration of ventricular systole. AS: Atrial systole.

and the sections of the different marginal curves as well as the mutual relation between these, and their duration.

The marginal curve of the aorta (see Fig. 1) is extremely constant and corresponds to Lewis (4) aortic pressure curve. When the semilunar valves open and the outflow of blood commences, the marginal curve takes an oblique, lateral course as one in the beginning straight line, which at the end of the systole, when the pressure in the ventricle begins to fall, passes over into a convex arc, which reaches its lateral point at the moment when the pressure becomes the same in the aorta and the ventricle. While the ventricular pressure thereafter falls evenly, the curve moves over towards the middle, and when the pressure has fallen sufficiently the systole comes to an end, the semilunar valves closing, whereby a valve-closure notch is produced. Then, during the diastole, the aortic margin continues medially in a straight line, which toward the end of the diastolic period takes an almost perpendicular course corresponding to the period of relaxation, until the next systole begins.

The marginal curve of the left ventricle (see Fig. 1) shows a distinct resemblance to the volume curve described by Straub (6). At the end of the lateral movement — that is to say at the end of the diastole, — there is seen a little, brief movement toward the middle, a notch; upon which the curve again for a very short distance takes a lateral course before it, systolic, turns in medial direction. This notch is due to the closing of the atrio-ventricular valves, which become pressed into the





Table 1.

Name	Interval between medial movement of ventricle and beginning of lateral movement of aorta.	Interval between beginning of QRS complex and begin- ning of lateral move- ment of aorta.	Length of space between mitral- valve notch and beginning of QRS complex.	Duration of presphygmie period.
	seconds:	seconds:	seconds:	seconds:
G. B. ....	0	0.06	0	0.06
I. B. I. ....	0	0.07		
» II. ....	0	0.06		
K. E. I. ....	0	0.06	0	0.06
» II. ....	0	0.06	0	0.06
G. N. I. ....	0	0.03	0.01 after	0.02
A. B. ....	0	0.04		
K. G. ....	0	0.06	0	0.06
E. G. ....	0	0.03	0	0.03
M. E. H. I. ....	0	0.07	0.1 before	0.08
» II. ....	0	0.07	0.02 after	0.05
» III. ....	0	0.07	0.02 after	0.05
» Ia. ....	0	0.06		
» IIa. ....	0	0.07	0.03 after	0.04
E. H. I. ....	0	0.06	0	0.06
» II. ....	0	0.04	0	0.04
E. M. ....	0	0.04	0.02 before	0.06
K. M. ....	0	0.07		
M. M. I. ....	0	0.06	0.01 after	0.05
» II. ....	0	0.06	0.02 after	0.04
A. N. I. ....	0	0.07	0	0.07
» II. ....	0	0.07		
K. N. I. ....	0	0.06	0.01 after	0.05
» II. ....	0	0.07	0.01 after	0.06
T. P. I. ....	0	0.07	0	0.07
» II. ....	0	0.07	0.02 after	0.05
R. P. I. ....	0	0.04		
» II. ....	0	0.06		
K. S. I. ....	0	0.06	0.02 before	0.08
» II. ....	0	0.07		
K. T. I. ....	0	0.04		
» II. ....	0	0.06	0	0.06
M. T. I. ....	0.03	0.04		
» II. ....	0	0.06	0.02 after	0.04
G. W. ....	0	0.04		
K. R. I. ....	0	0.06		
» II. ....	0	0.04	0	0.04
» III. ....	0	0.06	0.02 after	0.08

to the difference in time between the beginning of the QRS complex and the beginning of the lateral movement of the aorta, plus or minus the length of time which the mitral valve-closure notch falls before or after the QRS complex. As it will be seen from the fifth column, these values vary, for the twenty-five cases, from 0.02 second in one case and 0.03 second in another to between 0.04 and 0.08 second; which accords well with the values found by other investigators.

### Summary.

By simultaneous electrocardiography and kymography (with 36 mm grid diaphragm) of young subjects with sound hearts the author has been able to



From the Medical Department of Serafimerlasarettet, the Pharmacological Department of Karolinska Institutet and the Central Clinical Laboratory of Södersjukhuset, Stockholm.

## Macrocytosis in Acute Hepatitis and Pernicious Anemia. A Comparison Based on S30 Price-Jones' Curves.

With two Case Reports of Acute Hepatitis  
Complicating Pernicious Anemia.

By

GUNNAR LINDGREN.<sup>1</sup>

(Submitted for publication January 26, 1949.)

It is a well known fact that in *pernicious anemia* there are *anisocytosis*, *poikilocytosis* and an *increased mean red cell diameter*. The cause of these changes is generally attributed to the lack of a specific hemopoietic principle.

Changes in the blood picture are also to be found in a number of cases with disorders of the liver. Thus a relative *increase in the mean diameter of the erythrocytes* and an *anisocytosis* which rises with the increasing mean diameter, are to be observed in almost every case of acute *hepatitis* (12).

Hence the hematological changes of pernicious anemia and hepatitis offer certain similarities. In addition to this there is the fact that the liver probably occupies a central position in the pathogenesis of both disorders. It would therefore have seemed reasonable to suggest — as has already been done by several authors (3, 8, 16, 20, 22) — that macrocytosis in severe liver damage may be due to the liver having lost its power to *store* or to *utilize* and *release* the antianemic principle of pernicious anemia.

Extracts from the liver of patients who have been inadequately treated for pernicious anemia may not contain the active pernicious anemia principle (6, 9, 21). Schiff, Rich & Simon (18), however, have succeeded in obtaining active extracts from the liver of patients with cirrhosis of the liver and simultaneous megalocytic anemia, acute yellow atrophy of the liver, toxic hepatitis and other forms of damaged livers. Goldhamer, Isaacs & Sturgis (6), who have carried out similar experiments, have even been able to produce an active extract from a patient who died of acute yellow atrophy of the liver with severe macrocytic anemia. They found it «highly suggestive that, although the active principle may be present in the liver, if sufficient hepatic damage is present, this organ is unable to release the necessary substance for red cell development in a suitable form for utilization by the body tissues».

<sup>1</sup> Danderydsgatan 12, Stockholm.

Most of the investigations referred to above have been carried out with extracts from cirrhotic livers. It seems permissible to assume that an analogous reasoning may be applicable also in cases of acute hepatitis. There has been very little discussion about these acute cases in this connection, however, and it has not been possible to obtain any direct information from the papers hitherto published. Hence the following observations from two cases of pernicious anemia, complicated by hepatitis, may be of interest and likely to contribute to the knowledge concerning *the mechanism of macrocytosis*.

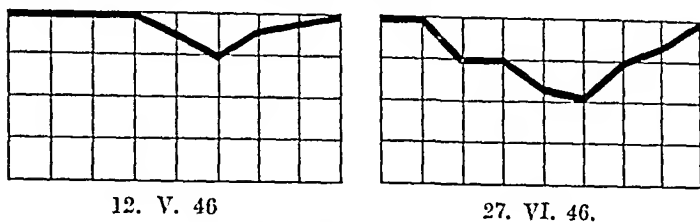


Fig. 1 a. Takata in case 1.

### Case Reports.

*Case 1.* Male, 59 years of age. The patient was healthy until April 1944, when pernicious anemia was discovered. The laboratory findings were typical: hyperchromic anemia, anisocytosis, increased mean red cell diameter, increased serum iron, histamine refractory achlorhydria, megaloblastic sternal marrow (fig. 1 b). Roentgen examination of the stomach disclosed no tumor. After injections of potent liver extract (8 ml pernaemon forte) he got a characteristic reticulocyte response with a rise from 0.5 to 25 %. There was also a typical rise in the hemoglobin values (Hgb) and the number of red blood corpuscles/mm<sup>3</sup> (R. b. c.).

During the rest of 1944 and during 1945 he visited the out-patient department several times and was treated with liver extract injections, either 2 ml pernaemon forte or 2 ml heptomin, every 3—4 weeks. When examined 27. XII. 45 Hgb<sup>1</sup> was 82 % and R. b. c. 3.4 mill.

After this the patient neglected to come for the usual monthly controls and did not return until 22. III. 46. Hgb had now fallen to 52 % and R. b. c. to 2 mill. He also showed signs of slight myelopathy. From 22. III. 46 to 12. IV. 46 during a stay in the hospital he was treated with altogether 16 ml pernaemon forte raising his Hgb to 76 % and R. b. c. to 3.5 mill. The reticulocyte peak was 11.8 %.

At the next visit in the out-patient department 11. V. 46 he had developed typical hepatitis<sup>2</sup> and was ordered to bed. He was slightly jaundiced (bilirubin in serum = 7.6 mg%) and complained of lassitude and loss of appetite. His stools were »claycoloured» and urine dark, Ehrlich's test for urobilinogenuria being strongly positive. Takata's reaction disclosed liver damage (fig. 1 a). When repeated later on, 26. VI. 46, the values from this test were still more pathologic despite the almost normalized serum bilirubin (1.1 mg%). After 31. VIII. 46 the patient once again failed to appear until 21. II. 47. In spite of his not having had any liver extract therapy since 12. IV. 46 only slight anemia had developed (Hgb 70 %, R. b. c. 2.9 mill.). A series of liver extract injections was planned, but after the first one (2 ml heptomin) the patient disappeared for another 5 months. This time his negligence resulted in a considerable decrease in the blood values, Hgb becoming 40 % and R. b. c. 2 mill. (30. VII. 47).

<sup>1</sup> 100 % = 16 g hemoglobin/100 ml blood.

<sup>2</sup> The possibility of an inoculation hepatitis must be taken into consideration, several hundreds of hepatitis patients being treated in the medical service and in the out-patient department during 1943—1946.

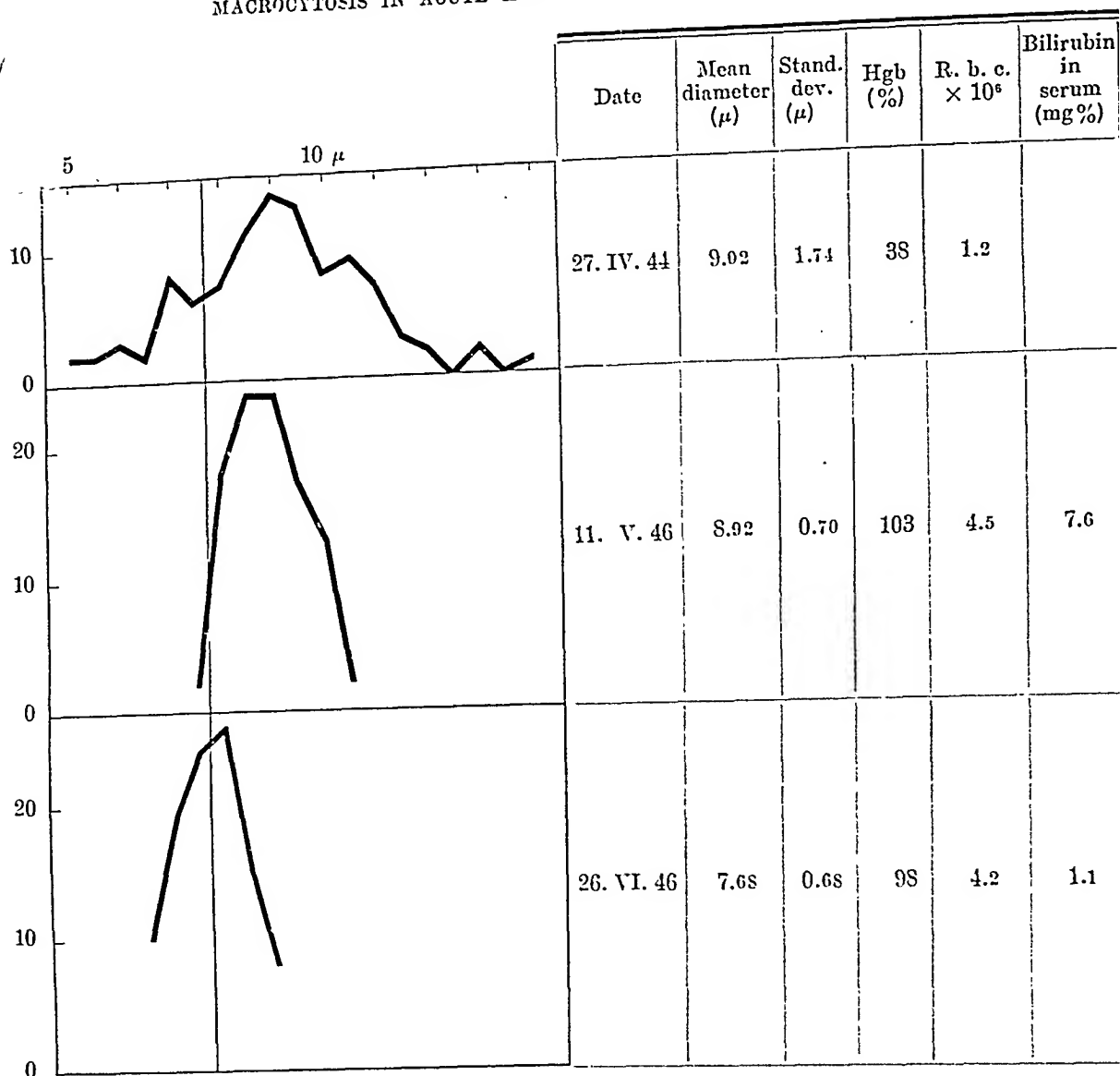


Fig. 1 b. Price-Jones' curves in acute hepatitis complicating pernicious anemia. *Case 1.* (male, 59 yrs).

*Abscissa* indicates erythrocyte diameter in  $\mu$ , *ordinate* number of red blood cells within each 0.5  $\mu$  group. Date of examinations, serum bilirubin, mean red cell diameter and its standard deviation ( $\sigma$ ), hemoglobin (Hgb) and number of erythrocytes/mm<sup>3</sup> (R. b. c.) simultaneously determined are tabulated to the right of figure. The vertical line at 7.68  $\mu$  indicates the average of the mean red cell diameter in 90 healthy subjects (5).

Pernicious anemia was discovered in April 1944, acute hepatitis diagnosed 11. V. 46. Though no treatment with liver extract was given 12. IV. 46—21. II. 47, the Price-Jones' curve was normalized when the hepatitis had subsided.

At the height of the hepatitis (11. V. 46) his Price-Jones' curve disclosed macrocytosis but only slight anisocytosis. Fig. 1 b also shows that when the hepatitis had subsided the curves had been normalized without the supply of any further extract.

*Case 2.* Female, 63 years of age. The patient was suffering from subchronic polyarthritis, which had first made its appearance in 1940. Pernicious anemia was discovered in August 1943. In this case, too, there was exactly the same complete symptom complex and criteria for the diagnosis as in case no. 1. After the discovery of the anemia she was treated regularly with liver extract injections (approximately 2 ml pernaemon forte every sec-

ond week). Towards the end of June 1945 gradually increasing jaundice developed with accompanying fatigability, lassitude and anorexia. She had no abdominal pains, however. The urine was dark, containing an excess of urobilinogen, the stools »clay-coloured». After a time she began also to complain of diarrhea and itching of the skin. The patient was kept at home at first and was not admitted to the hospital until 7. VIII. 45. Now there was no urobilinogenuria, the urobilinuria had diminished and the stools were acholic. The liver was not palpable. Serum phosphatase was normal (9 U/100 ml serum), a value strongly suggesting hepatitis. The highest bilirubin value obtained during the course of the disease (26.1 mg%) was reached on 16. VIII. At this time all joint pains had completely disappeared. Even on the day when she was discharged from the hospital (29. VIII. 45) to go on resting at home, the bilirubin value was considerably increased (10 mg%).

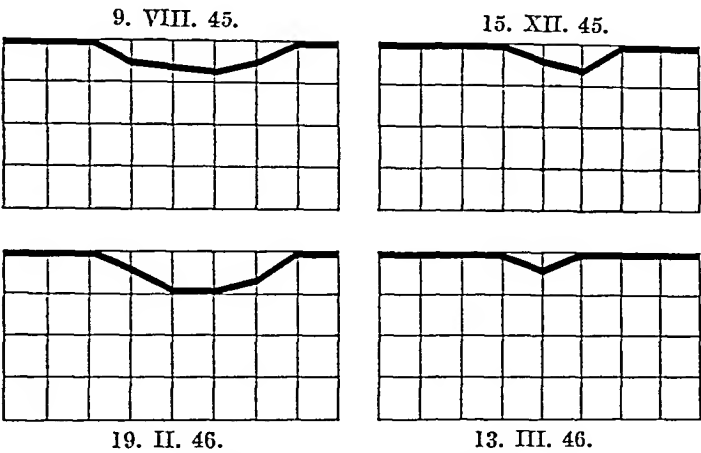


Fig. 2 a. Takata in case 2.

The last liver extract injections previous to the development of hepatitis were given on 5. IV, 12. V, 18. VI and 17. VII. 45. From 17. VII. 45 to 26. III. 46 the patient received no liver extract therapy but was given considerable doses of iron (from 18. II. to 26. III. 46) without any effect (fig. 2 b). The serum iron was 137  $\gamma$  % (15. III. 46). As soon as full doses of liver extract were given (from 26. III. 46) the situation changed and already on 23. IV. 46 Hgb had reached 74 % and R. b. c. 3.1 mill.

The following course was uneventful, her anemia being kept rather well under control by regular liver extract injections. At her last visit in the out-patient department (Sept. 1948) Hgb was 82 %, R. b. c. 3.9 mill./mm<sup>3</sup> and mean erythrocyte diameter 8.56  $\mu$ . The diameters of the red cells were distributed as follows:

Diameter ( $\mu$ )	7	7.5	8	8.5	9	9.5	10	10.5	11
Number of red blood cells	3	11	26	17	29	7	4	2	1

Cholecystography did not disclose any abnormality, neither did the thymol test or Takata deviate from normal. Serum contained 42  $\gamma$  % iron.

Comment.

*Case 1 demonstrates that macrocytosis in hepatitis cannot be due to the inability of the liver to store the hemopoietic principle, the Price-Jones' curve becoming normalized during the recovery period of the hepatitis without any supply of liver extract.*

The antipernicious anemia factor (= Castle's hematinic principle) is supposed

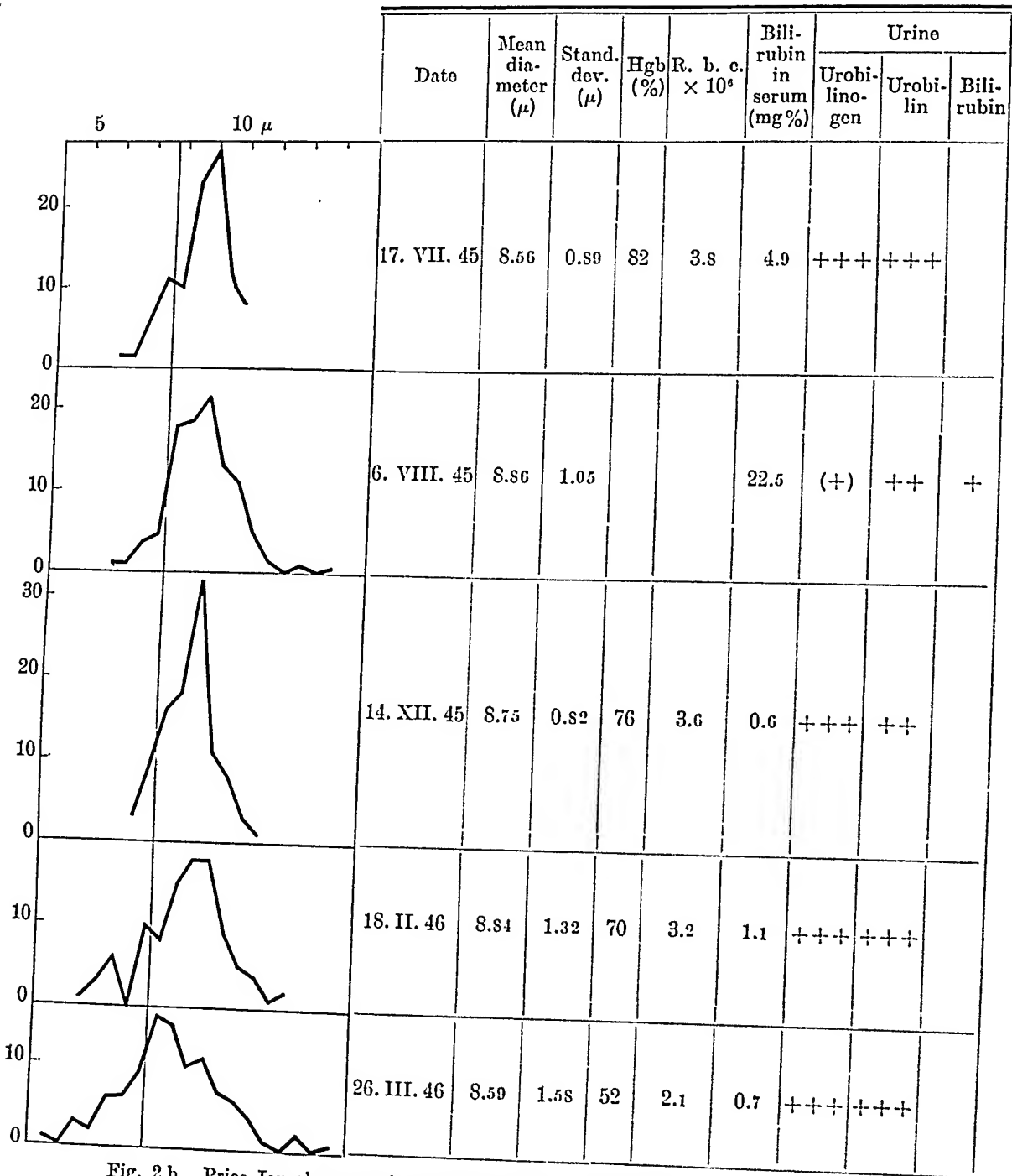


Fig. 2 b. Price-Jones' curves in acute hepatitis complicating pernicious anemia.  
Case 2. (female, 63 yrs).

Same indications as in fig. 1 b.  
Pernicious anemia was discovered in August 1943, acute hepatitis diagnosed in June 1945. No treatment with liver extract was given 17. VII. 45—26. III. 46.

to be stored in other organs besides the liver. Consequently the case does not exclude the possibility that macrocytosis in hepatitis is not due to the failure of the liver to utilize and release the principle.

In case 2 the highest mean diameter and bilirubin values were obtained almost simultaneously (6. VIII. 45 (fig. 2 b)). Despite the patient not having received any liver extract injection since 17. VII. 45, the anisocytosis had not increased after the hepatitis had subsided (14. XII. 45). No obvious anemia had developed either. Only after another 2 months' pause in the treatment with liver extract did there appear any manifest increase in the anisocytosis which was followed by a rapid drop in the patient's Hgb and R. b. c. values during the next month. Iron, administered during this period, could not prevent the relapse of her anemia. As soon as full doses of liver extract were given, however, the situation changed. Already on 23. IV. 46 Hgb had reached 74 % and R. b. c. 3.1 mill.

Owing to the long latency before anemia again developed after the cessation of liver treatment, it must be considered unlikely that the increase of the mean diameter at the height of the patient's hepatitis could be attributed to the inability of the liver to store the hemopoietic principle. As in case 1 it is not possible to conclude from this test either whether macrocytosis in hepatitis may be caused by a failing of the liver to utilize and release the principle.

A deficiency of this kind in the liver function, however, seems hardly able to give an exhaustive explanation as to the origin of macrocytosis in hepatitis, the differences in the peripheral blood picture of hepatitis and of pernicious anemia apparently being rather too great. Schalm (17) assumes: »In pernicious anemia there is constantly an elevated colour-index, an elevated volume-index, important anisocytosis and very distinct poikilocytosis. In most cases of hepatic damage however — perhaps with the exception of the group of cirrhosis of the liver — neither the colour-index nor the volume-index are elevated. Another remarkable difference is the moderate anisocytosis and the almost complete absence of abnormal poikilocytosis.» Besides Schalm several other writers (1, 2, 3, 4, 7, 10, 11, 13, 14, 19, 22) have published similar observations, based chiefly, however, on investigations of only one or a few cases. Mogensen (14), however, states that »on the whole the literature on this question gives the impression, that an indubitable difference has not been proved between the distribution curves in diseases of the liver and in pernicious anaemia».

Our observations from a comparison between the Price-Jones' curves in one series of uncomplicated hepatitis cases and another of pernicious anemia further exemplify the differences between the two disorders.

Fig. 3 illustrates the correlation between the mean diameter and the simultaneously determined standard deviation<sup>1</sup> in 685 Price-Jones' curves from 220 acute cases of hepatitis, in 56 curves from 31 cases of pernicious anemia and finally in 89 curves from as many healthy subjects.

The abscissa indicates the mean diameter, the ordinate the standard deviation in the curve on which the mean diameter has been calculated. The hepatitis values are too numerous to be given individually in the figure, and therefore only the regression line (A) for the correlation in question has been inserted. The lines parallel with it indicate the boundaries  $\pm 2 \sigma$  and  $\pm 2.5 \sigma$ . The observations from pernicious anemia cases, how-

<sup>1</sup> As in our method only one diameter of each cell is measured it will not be advisable to consider anisocytosis and standard deviation as identical expressions without further analysis. A high grade poikilocytosis may raise standard deviation considerably.



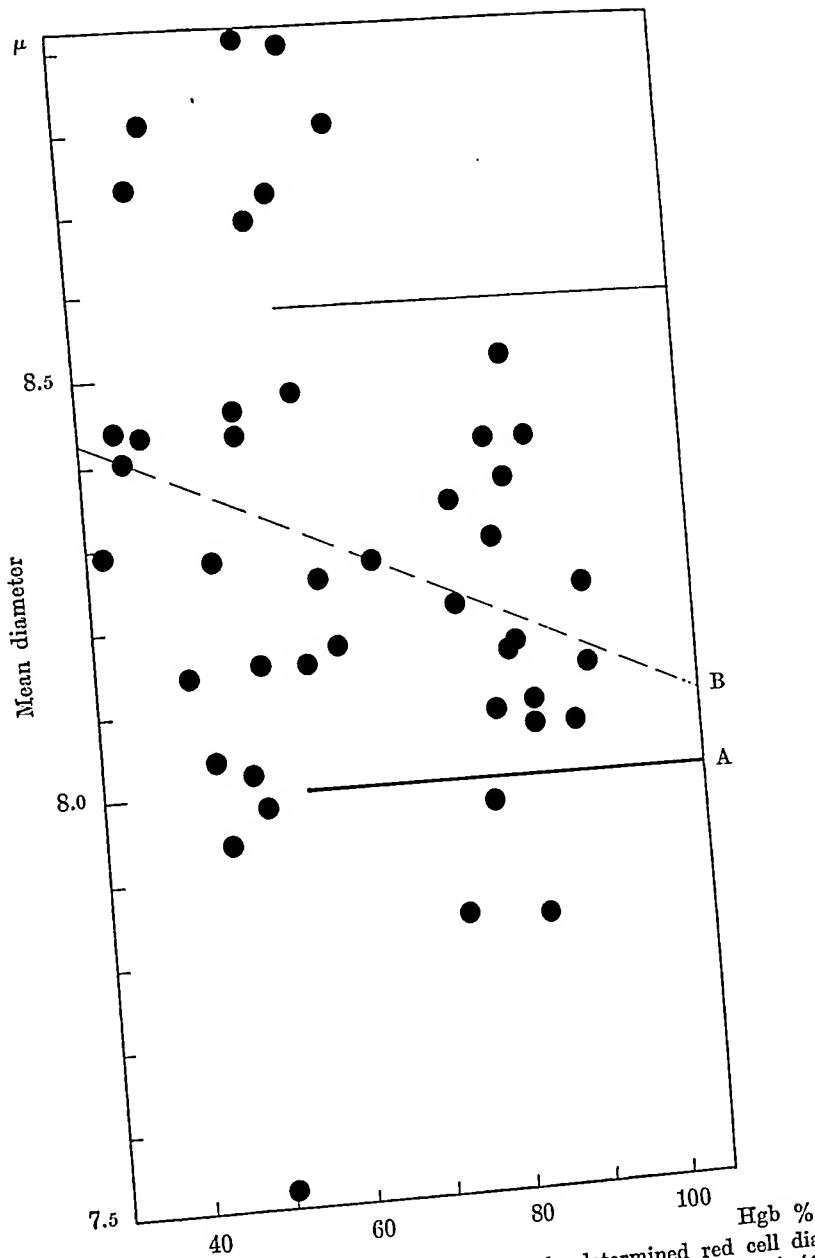


Fig. 4. Hemoglobin percentage (abscissa) and simultaneously determined red cell diameter in  $\mu$  (ordinate). Comparison between *acute hepatitis* (regression line A) and *pernicious anemia* (●; regression line B).<sup>1</sup>

The thin continuous line parallel with line A indicates  $+2\sigma$ .

and in *hepatitis* even taking into consideration that the *pernicious anemia* group contains far more cases with low Hgb values than the *hepatitis* one (fig. 5).

<sup>1</sup> Regression equation A:  $y = 7.86 + 0.001 x$ ;  $b = 0.001 \pm 0.002$ ;  $r = 0.04 \pm 0.07$ ;  $n = 221$ ;  
B:  $y = 8.57 - 0.005 x$ ;  $b = -0.0045 \pm 0.0025$ ;  $r = -0.27 \pm 0.139$ ;  
 $n = 45$ .

# MACROCYTOSIS IN ACUTE HEPATITIS AND PERNICIOUS ANEMIA.

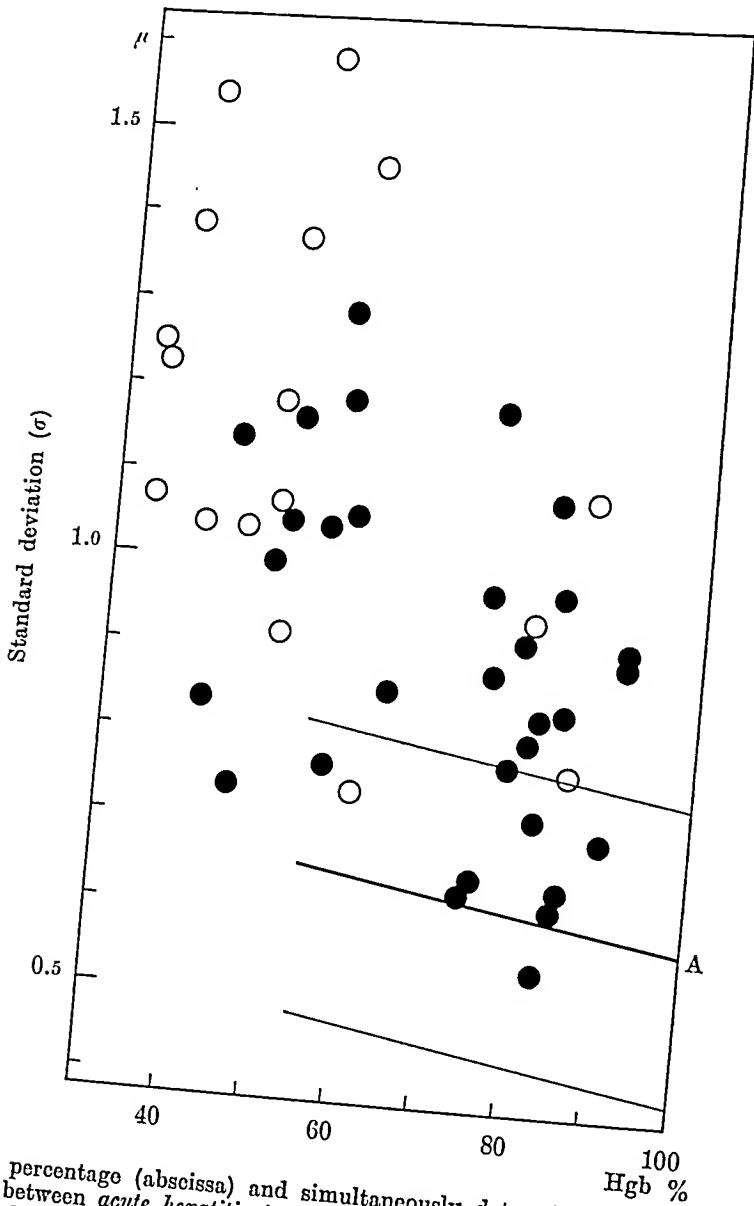


Fig. 5. Hemoglobin percentage (abscissa) and simultaneously determined standard deviation (ordinate). Comparison between *acute hepatitis* (regression line A; 213 determinations) and *pernicious anemia* (○, ●); ○ indicates freshly discovered cases, which had not yet been treated at the time when the determinations were taken; ● indicates other cases. The thin continuous lines parallel with line A indicate  $\pm 2 \sigma$ .

It has been possible to establish a significant correlation between Hgb (x) and standard deviation (y) in pernicious anemia (correl. coeff. =  $-0.49 \pm 0.114$ ). The corresponding correlation in the hepatitis group is of very low order (correl. coeff. =  $-0.167 \pm 0.067$ ; regr. eq.  $y = 0.725 - 0.0015 x$ ).

The statistical implication of the boundary lines  $\pm 2 \sigma$  is that out of the 213 hepatitis values  $\leq 10$  (9.7) can be expected to be found outside the  $\pm 2 \sigma$  limit. If the values from the pernicious anemia cases had been distributed in a similar manner, only one of the 24 values from cases with Hgb  $> 60\%$  would have fallen

outside the  $\pm 2 \sigma$  boundary. Fig. 4, however, shows that no fewer than 15 of these 24 are situated  $> 2 \sigma$  from the regression line of hepatitis. Chi-square analysis shows that the difference between the hepatitis and the pernicious anemia group in the above mentioned respect is statistically significant ( $\chi^2 = 77.6$ ;  $P < 0.001$ ).

Table 1.

*Percentage of Cells in Extreme Diameter Classes  $< 6.5$  and  $> 10.5 \mu$ .*

Comparison between normal subjects and cases of acute hepatitis and pernicious anemia divided into two groups according to hemoglobin value.

	Hgb 50—79 %			Hgb $\geq 80$ %		
	$< 6.5 \mu$	$> 10.5 \mu$	n	$< 6.5 \mu$	$> 10.5 \mu$	n
Normal .....				0.3	1 —	9,000
Acute hepatitis .....	0.1	—	4,000	0.2	<sup>2</sup> 0.02	18,800
Pernicious anemia .....	3.7	3.3	900	1.0	4.4	800

n = number of cells used for calculation of percentage; 100 cells measured in each case.

Table 1 shows yet another difference of the peripheral blood between pernicious anemia and acute hepatitis. It will be seen that in the former disease there are more cells in the extreme diameter classes than in the latter.

In fig. 6 the regression line has been inserted for the correlation between the Hgb percentage and the simultaneously determined number of red blood cells/mm<sup>3</sup> in acute hepatitis (—). The boundaries  $\pm 2 \sigma$  are indicated in the usual way. The corresponding determinations in a number of pernicious anemia cases have been marked individually (●). Their regression line is indicated by — — — —.

The difference in the position of the two regression lines does not contradict the assumption put forward by several writers that the enlarged blood cells in acute hepatitis and in pernicious anemia have different shapes.

### Acknowledgements.

The author is indebted to the foundation »Therese and Johan Anderssons Minne» for financial support, to L. Goldberg, M. D. Pharm. Dept. Karolinska Institutet, and G. Hammarsten, M. D. Södersjukhuset, for advice during the course of this work. Practically all the measurements of the erythrocyte diameter in this paper have been made by Febe Gunvall.

### Summary.

Anisocytosis and increased mean red cell diameter are characteristic features in the blood picture of both pernicious anemia and acute hepatitis. Consequently

<sup>1</sup> Out of 9,000 cells 6 had a diameter of 10—10.5  $\mu$ .  
<sup>2</sup> Out of 18,800 cells 107 had a diameter of 10  $\mu$  and 25 of 10.5  $\mu$ .

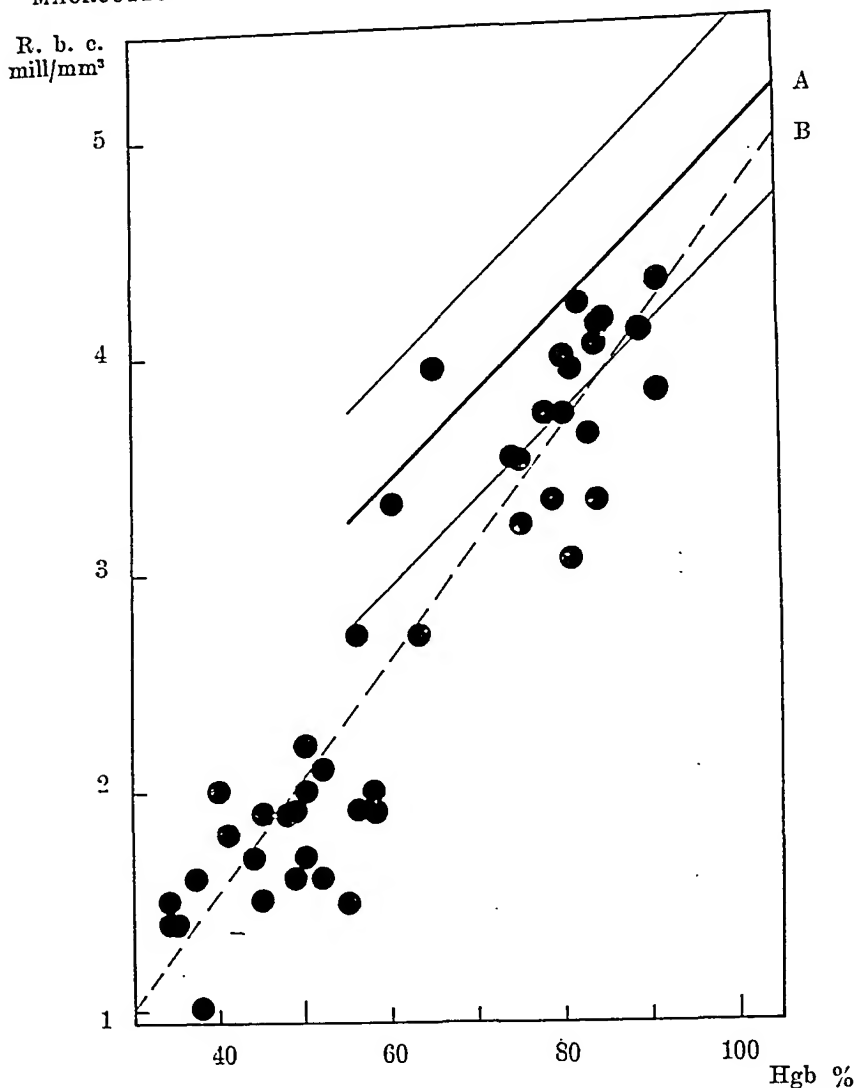


Fig. 6. Hemoglobin percentage (abscissa) and simultaneously determined number of red blood cells/mm<sup>3</sup> (ordinate). Comparison between *acute hepatitis* (regression line A) and *pernicious anemia* (●; regression line B).<sup>1</sup>

The thin continuous lines parallel with line A indicate  $\pm 2 \sigma$ .

several authors have suggested that macrocytosis in severe liver damage may be due to the liver having lost the power to *store* or to *utilize* and *release* the anti-anemic principle of pernicious anemia.

Two cases of pernicious anemia complicated by acute hepatitis are reported. The first one of these cases demonstrates that macrocytosis in hepatitis cannot be due to the inability of the liver to *store* the hemopoetic principle, the Price-Jones' curve becoming normalized during the recovery period without any supply of liver extract. As this principle is supposed to be stored in other organs besides the liver, the case, however, does not exclude that macrocytosis in hepatitis is not due to the failure of the liver to *utilize* and *release* the principle.

<sup>1</sup> Regression equation A:  $y = 1.11 + 0.038x$ ;  $b = 0.038 \pm 0.002$ ;  $r = 0.83 \pm 0.021$ ;  $n = 225$ ;  
B:  $y = 0.053x - 0.56$ ;  $b = 0.052 \pm 0.003$ ;  $r = 0.93 \pm 0.021$ ;  $n = 44$ .

The details of the Price-Jones' curves from 220 cases of acute hepatitis, 31 cases of pernicious anemia and 89 healthy subjects have been studied and the correlation determined within each of the groups mentioned between mean diameter and standard deviation (fig. 3), between hemoglobin percentage and mean diameter (fig. 4), between hemoglobin percentage and standard deviation (fig. 5) and finally between hemoglobin percentage and number of red blood cells/mm<sup>3</sup> (fig. 6). The differences in the peripheral blood picture of acute hepatitis and pernicious anemia were found to be rather great in these respects. Consequently it seems hardly probable that macrocytosis in hepatitis may be due to a simple inability of the liver to utilize and release the antianemic principle of pernicious anemia.

### References.

1. Benhamou, Ed. & Nouchi, A.: *Presse méd.* 1937, *45*, 1027. — 2. Bock, H. E.: *München. med. Wehnschr.* 1934, *81*, II, 1686. — 3. van Duyn, J.: *Arch. Int. Med.* 1933, *52*, 839. — 4. Gamna, C.: *Klin. Wehnschr.* 1933, *12*, 348. — 5. Goldberg, L., Gunvall, F., Hammarsten, G. & Lindgren, G.: *Acta med. Scandinav.* 1948, *132*, 238. — 6. Goldhamer, S. M., Isaacs, R. & Sturgis, C. C.: *Am. J. M. Sc.* 1934, *188*, 193. — 7. Gram, C.: »Undersøgelser over de røde Blodlegemers Størrelse hos Mennesket.» Copenhagen 1883. — 8. Hijmans van den Bergh, A. A. H. & Kamerling, A. W. C. G.: *Nederl. tijdschr. v. geneesk.* 1934, *78*, 4432. — 9. Ivy, A. C., Richter, O. & Kim, M. S.: *Am. J. Physiol.* 1932, *101*, 59. — 10. Jørgensen, S. & Warburg, E. J.: *Acta med. Scandinav.* 1927, *66*, 109. — 11. Jørgensen, S. & Warburg, E. J.: *Acta med. Scandinav.* 1927, *66*, 135. — 12. Lindgren, G.: *Acta med. Scandinav.* 1949, *133*, 322. — 13. Malamos, B.: *Deutsches Arch. f. klin. Med.* 1935, *177*, 209. — 14. Mogensen, E.: »The Size of the Red Blood Cells.» Copenhagen 1938. — 15. Möller, K. L.: *Acta med. Scandinav.* 1944, *119*, 133. — 16. Rosenberg, D. H. & Walters, A.: *Am. J. M. Sc.* 1936, *192*, 86. — 17. Schalm, L.: *Acta med. Scandinav.* 1937, *93*, 512. — 18. Schiff, L., Rich, M. L. & Simon, S. D.: *J. Clin. Investigation* 1937, *16*, 666. — 19. Schulten, H.: »Lehrbuch der klinischen Hämatologie.» Leipzig 1939. — 20. Watkins, C. H.: *Proc. Staff Meet., Mayo Clin.* 1935, *10*, 432. — 21. Wilkinson, J. F. & Klein, L.: *Quart. J. Med.* 1934, *27*, 341. — 22. Wintrobe, M. M. & Shumacker, H. S.: *Bull. Johns Hopkins Hosp.* 1933, *52*, 387.
-





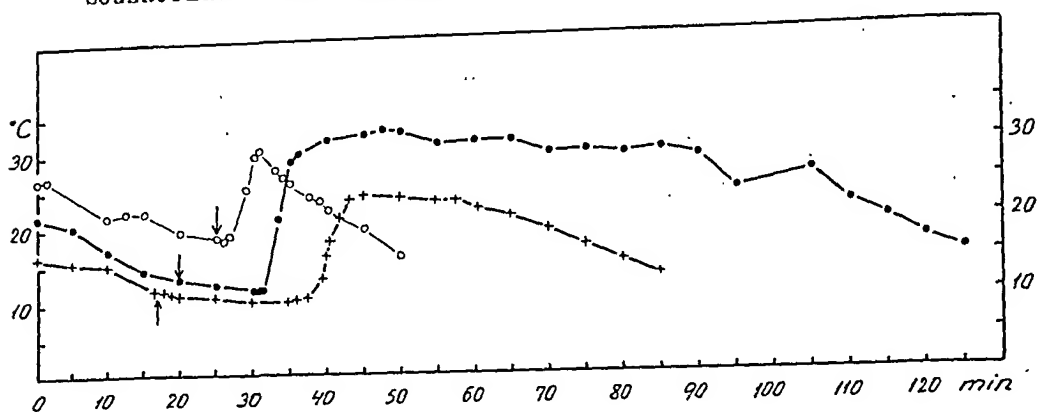


Fig. 1.

- Finger-pulp temperature under local cooling and response to intravenous injection of 5 ml 10 % tetra-ethyl-ammonium bromide in a normal individual.
- Finger-pulp temperature during local cooling and the response to intravenous injection of 5 ml 10 % tetra-ethylammonium bromide in the patient Nov. 10th 1947.
- +—+ Finger-pulp temperature during local cooling and the response to intravenous injection of 5 ml 10 % tetra-ethyl-ammonium bromide in the patient Oct. 29th 1948.
- ↓ Time for injection.
- abscissa: time in minutes.
- ordinate: pulp temperature in degrees centigrades.

#### *Indirect heating by the method of Gibbon & Landis (1932):*

The right hand warms normally but after a prolonged latent period. The left foot cannot be warmed indirectly even if the patient is bathed in sweat by the heating.

For two months the patient was treated with Finsen-light baths, remedial gymnastics and prostigmin. He became more and more enfeebled, and by degrees stiff in all joints; the skin became tight all over, and he developed difficulty in swallowing. 14 months after the onset of the illness the left arm began slowly to improve and strength began to return so that he could take short walks alone. On re-examination 16 months after onset, movements of all joints were restricted, the skin of the left arm was normal, but everywhere else it was hard, smooth and shiny, especially on the chest, neck and right upper arm, with increased sweating of the hands and feet. During this period he was treated with massage, active movements, and for a short time with per corten (Ciba) (1 ml intramuscularly daily for 12 days). In the two months after this the stiffness of the joints almost disappeared and the strength of the muscles of the back and abdominal wall improved, so that he is now in a relatively good condition.

The various laboratory examinations show nothing new.

*Biopsy of muscle* Sept. 21st 1948 (Erna Christensen): slight degeneration of a part of the myo-fibrils, since the individual bundles contain fibres of widely varying thickness. No lymphocyte infiltration is found and only moderate hypertrophy of the interstitial connective tissue.

*Biopsy of skin* Sept. 21st 1948 (Erna Christensen): Atrophy and deficient cornification of the epidermis, flattening of the papillae, hypertrophy of the collagenous connective tissue in the chorium, degeneration of the hair-follicles but apparently



normal sweat and sebaceous glands. In many parts lymphocytic infiltration, both perivascular and around the degenerated hair-follicles, is seen.

*Pulp-temperature during tetra-ethyl-ammonium blockade* Oct. 29th 1948: latent period 21 minutes. After rising to 24° C the temperature is maintained at this level for 13 minutes (Fig. 1).

### Discussion.

The serum injection must be considered to be the cause of the pathological condition described. The onset of the symptoms after this injection followed the classical course of serum sickness. Muscular changes after serum treatment corresponding clinically to those found in our patient and included in the picture radiculitis, neuritis and polyneuritis have also been observed previously. The earliest certain description of these changes appears in the French literature (Gangolphe & Gardere 1908). Subsequently case records were published in many countries and a number of critical reviews have appeared in which the authors have attempted to systematise the previous descriptions (Petit 1925, Allen 1931, Bineau 1938, Bennett 1939). A case very like the present one except for the absence of skin manifestations, and progressing over a period of 15 years, is described by l'Hermitte (1938). The occurrence of peripheral cyanosis after serum-sickness has also been reported previously and was ascribed to abnormal functioning of the autonomic nervous system (Bineau 1938).

The observed changes must be attributed to an allergic reaction, either at the sites of the manifestations or in the centres influencing the function of major parts of the organism, *e. g.* nerves and ductless glands. In our patient there is evidence of damage to somatic nerves (trigeminal hyperesthesia) and to the autonomic innervation of the blood-vessels (abnormal reactions to indirect warming and tetra-ethyl-ammonium blockade).

The electromyographical studies and the increased sensitivity to acetylcholine indicate that the muscular disturbances are of peripheral origin, but whether neurogenic or myogenic cannot be distinguished. It is possible that they are due to dysfunction of the autonomic regulation of the blood supply of the muscles. In experiments on animals it has been shown that section of parasympathetic and sympathetic fibres can produce muscular atrophy (Kuré *et al.* 1927) and in man it has been demonstrated that muscular fatigue sets in earlier under such circumstances (Altenburger 1931). The changes in the skin, which together with the muscular abnormalities have dominated the picture, may perhaps be of local origin, but dysfunction of the autonomic nervous system is as likely a cause. Both the autonomic disturbance demonstrated and the fact that one extremity escaped both the skin and muscular disorders are points in favour of the latter causation.

While the muscular changes resemble those previously reported after serum injection, skin manifestations of the character here described have not been previously reported after serum treatment, which would indicate that it is not the allergic reaction itself but the damage to cells controlling the normal metabolism of the skin and muscles which is the cause of the syndrome. The latter throughout

its development corresponds exactly to the symptom-complex termed sclerodermia diffusa.

The first three phases — prodromata, oedema and induration — are passed through quickly. Some isolated areas are progressing towards the terminal atrophic phase. It must be added that only rarely have the muscular symptoms been reported as occurring so early and so predominantly. (On Sclerodermia diffusa: S. Ehrmann & S. R. Brünauer, *Handbuch der Haut- u. Geschlechtskrankheiten* VIII/2, 717—858, Berlin 1931.) Pathological pictures such as the present have previously been described as dermatomyositis. It is not possible to decide which term is the more correct; they are both expressions of our defective understanding of the essential nature of the disease.

It is seen that a picture like sclerodermia can be produced on an allergic basis. As the observed prodromata of sclerodermia consist of fever, irritability, urticaria, erythemata and rheumatic pains and swellings of the joints, a picture completely corresponding to that of serum sickness, it is probable that an allergic process is not uncommonly the cause of these manifestations. Besides the changes found in our patient there is much to indicate that damage to nerve cells is the link between the primary alterations and the appearance of the symptoms. The changes are often confined to the area supplied by a nerve-trunk and when one extremity is affected a sharp demarcation at the mid-line can as a rule be seen. Haxthausen (1947) has shown that when skin from an area of morphoea (sclerodermia circumscripta) is transplanted to a healthy area and vice versa, the sound transplant is converted to sclerodermic tissue while the abnormal skin becomes healthy. This also indicates that the disturbances are of nervous origin.<sup>1</sup>

### Summary.

From a case of sclerodermia after serum treatment and the results of investigations upon the patient it is suggested that sclerodermia is often due to nervous disturbances excited by an allergic reaction.

### References.

- Allen, J. M.: *Lancet* 1931, 2, 1128. — Altenburger, H.: *Ztschr. gesammte Neurologie u. Psych.* 1931, 132, 490. — Bennett, A. E.: *J. A. M. A.* 1939, 112, 590. — Bineau, R.: Thèse, Paris 1938. — Buchthal, F. & L. Engbæk: *Acta Psych. et Neurol.* 1948, 23, 3. — Gangolphe & Gardère: *Lyon méd.* 1908, 110, 497. — Gibbon, U. H. & E. M. Landis: *J. Clin. Invest.* 1932, 11, 1019. — Haxthausen, H.: *Acta derm. venerologica* 1947, 27, 352. — Kurée, K., T. Imagawa, S. Hatano & Y. Sunaga: *Z. exper. Med.* 1927, 54, 351. — l'Hermitte, L.: *Rev. Neurol.* 1938, 69, 375. — Petit, G.: Thèse, Nancy 1925. — Skouby, A.: *Acta med. scand.* 1949, 134, 335.

<sup>1</sup> I am indebted to Professor Mogens Fog for permit to examine the patient when he for a time was treated in the neuro-medical department of the Rigshospital, Copenhagen.

From the Medical Clinic, Serafimer Hospital, Stockholm  
(Head: Professor A. Kristenson), and  
the Department of Medicine, District Hospital, Östersund, Sweden  
(Head: I. Lundholm. M. D.).

## The Electrocardiogram in Hypocalcemia with Special Reference to the T-wave.

By

OLOF LJUNG.<sup>1</sup>

(Submitted for publication February 12, 1949.)

It is well known that hypocalcemia is common in children showing spasmodophilia. In adults it is found in post-operative and idiopathic hypoparathyroidism. Hypocalcemia may also accompany enterogenous disturbances such as sprue or coma hepaticum as well as the final stages of a chronic nephritis. If the aim is to study the electrocardiographic changes produced by hypocalcemia, hypocalcemia due to hypoparathyroidism is suited best because the other forms of this disease are associated with severe disturbances which may also influence the electrocardiographic pattern.

The appearance of the electrocardiogram (ecg) in hypocalcemia has engaged the interest of many authors. The first publications on this subject dealt mainly with the appearance of the ecg of children showing spasmophilia. Most of the early authors (Morgenstern, 1914, Schiff, 1923—1924, Doxiades & Vollmer, 1927, and others) wrote that the ecg of children showing spasmophilia was characterized by a high T-wave which was often peaked. Carter & Andrus (1922) were the first to bring forward evidence that spasmophilia produced prolongation of the Q—T interval. The majority of later authors supported this view (Aschenbrenner & Bamberger, 1935, Mannheimer, 1939). Other changes viz. a short conduction time, changes in the configuration of the T-waves and in the QRS complex which have occasionally been observed by some authors, do neither occur regularly nor are they characteristic of hypocalcemia. Several later investigators, however, have supported the view that the T-wave is increased and peaked in hypocalcemia (Migliori, 1938, Nádrai-Pecs, 1941). Also flattened T-waves have been observed in a few cases (Aschenbrenner & Bamberger, 1935).

As regards hypocalcemia in children the opinion seems at present to be that it produces prolongation of the Q—T interval. Concerning the configuration of the T-waves in these cases, the authors are not agreed. This applies also to hypo-

<sup>1</sup> Lasarettet, Karlstad (Sweden).

calcemia in adults though in this case there is more controversy about the question whether the T-wave is normal or abnormally low.

Several authors have reported that a prolonged Q—T interval is a typical feature of the ecg in hypocalcemia in adults (Carter & Andrus, 1922, Hecht & Korth, 1937, Barker et al., 1937, and others). Most of them claimed that hypocalcemia did not produce any other characteristic electrocardiographic changes.

Marzahn (1934, 1935) reported a case of post-operative tetany in which the T<sub>1</sub>-wave was slightly negative and the T<sub>2</sub>-wave low. He referred these changes to a myocardial lesion caused by the tetany. In two groups of 4 cases of hypocalcemia which came under their personal observation, Justin-Besançon & Laroche (1943), and Cellina & Selvini (1946) each found abnormal T-waves in one case. Hoesch (1939) reported one case of hypocalcemia in which the T-waves were abnormal. He wrote that he had often found low or iso-electric T-waves in the presence of hypocalcemia. Several textbooks also state that the T-wave is often either low or iso-electric in hypocalcemia (Jores, 1942, Sherf & Boyd, 1945, and others). According to Rasmussen (1946) it may also be negative.

Heggin & Holzman (1937) reported 8 case of post-operative hypocalcemia. Hecht & Korth (1937) discussed 12 cases of post-operative and 11 cases of idiopathic tetany. They did not identify any typical changes in the T-waves. (There was obviously only one instance in either group in which the T-waves were abnormal.) Admittedly, in some of these authors' cases the serum calcium was but slightly reduced. However, if all the cases of these two studies are taken together, the blood serum calcium content was below 7.5 mg% in 14, the degree of hypocalcemia being in some of them almost the same as that reported by the other authors mentioned above who found abnormal T-waves in the ecgs of some of their patients.

Fernbach & Szandany (1940) described a case of hypocalcemia in which normal T-waves alternated with abnormal ones in ecgs taken at intervals of a few days, whilst the serum calcium values did not change. I have observed one case of hypocalcemia due to chronic nephritis and two cases of post-operative hypocalcemia in which normal T-waves alternated with abnormal ones in the course of one day (Ljung, 1945). As the serum calcium rose the T-waves became normal and did not show any instability. These observations has led me to the suggestion that, apart from a prolonged Q—T interval and abnormal T-waves, the ecg in hypocalcemia may be characterized also be a marked instability of the T-wave. ✓

## Personal Studies.

### *Material and Technique.*

The purpose of this investigation was to study the appearance of the ecg in hypocalcemia giving special consideration to the behaviour of the T-wave. As mentioned above, the postoperative and idiopathic types of hypocalcemia are best suited for such a study. Since these cases are comparatively rare it is within a reasonable period of time very difficult to collect sufficient material for study.

The normal values of the blood serum calcium content range between 9 and 11 mg%. Only marked hypocalcemia produces typical electrocardiographic changes. In this study therefore all cases were excluded in which the serum calcium values were above 7.5 mg%.

The series here presented comprises 28 cases. In 1 of them hypocalcemia was due to an enterogenous disturbance, in 7 to chronic nephritis, and in 20 there was post-operative hypocalcemia. In studying these cases particular attention was given to the last mentioned group including 18 women and 2 men. Their ages ranged between 17 and 61 years with an average age of 40 years. In 18 of them I have on several occasions personally taken the eegs.

The eegs were taken with the aid of the electrocardiograph »Triplex» (system Elmquist) which is commonly used in Sweden. As a rule, only limb leads were used and recorded. The tracings were evaluated on the basis of the standard criteria. A line going either through the T—P or U—P levels was chosen as iso-electric level. The amplitude of the T-wave was measured from this line to the middle of the contour at the top of the P- or T-waves. The measurements were made with an accuracy of  $\frac{1}{2}$  millimeter, 1 cm corresponding to 1 millivolt.

As a rule, three eegs were taken when the serum calcium values were lowest and before applying any therapeutic measures. In some cases the tracings were made in the course of two successive days; in others they were made on one day at intervals varying between half an hour and two hours. The conditions of the examinations were always the same, *i. e.* the patient was examined on fasting and after having rested five minutes before each examination. In most cases three eegs were also taken when the serum calcium values were restored to normal in response to treatment with vitamin D, the conditions of the examination being the same as those described above.

On exercise eegs were taken either two or three minutes after the patient had run up and down Nylin's staircase at a moderate pace five times or after any similar exercise.

Ergotamine was administered in the form of »Gynergen-Sandoz». The eegs were taken 45 minutes after the subcutaneous injection of  $\frac{1}{4}$  mg Gynergen (in case 3 the tracings were made 30 minutes after the administration of this drug).

## Results.

### *I. Post-operative hypocalcemia.*

In 2 cases of post-operative hypocalcemia (cases 19, 20) the first examination already revealed signs suggestive of hypothyreosis. In one case (case 18) hypothyreosis was diagnosed later. Since hypothyreosis often produces changes in the electrocardiographic pattern, in the T-waves in particular, cases 19 and 20 were not suited for a study of the eeg in hypocalcemia. Abnormal T-waves in Leads I and II were found in both cases. In case 18 the T<sub>1</sub>- and T<sub>2</sub>-waves were markedly inverted during the presence of hypothyreosis.

*P-wave, P—Q interval, QRS-complex.*

In the remaining 18 cases neither the P-wave, P—Q interval nor the QRS complex showed anything abnormal when the serum calcium was reduced. Neither were there any changes identifiable when the values of the serum calcium had become normal. These observations are in agreement with the generally accepted opinion as to the appearance of the eeg in hypocalcemia in adults and need no further comment.

*Q—T interval.*

The Q—T interval was in all cases prolonged when the serum calcium values were lowest. As the serum calcium rose the Q—T interval became normal. In one case (case 8), however, though being appreciably shorter, it remained somewhat prolonged (+ 0.05). In measuring the upper limits of the normal Q—T interval the formula  $Q-T = 0.2 \times R-R + 0.22$  devised by me was applied (Ljung, 1948). To determine the average value of the normal Q—T interval I suggested the formula  $Q-T = 0.2 \times R-R + 0.18$ . The values of the prolongation of the Q—T interval as determined from this equation varied between 0.05 and 0.30 seconds, the average value of the prolongation being 0.10 seconds.

*S—T segment.*

The S—T segment did not show any abnormal deviation to the iso-electric line in the group of cases here discussed.

*T-wave.*

Since the T-wave in Lead III shows great variations also under normal conditions, only T-waves in Leads I and II were studied. As a matter of fact, the literature reviewed above, also deals only with the latter. T-waves with an amplitude of less than 1 mm were in this study looked upon as abnormal. This criterion corresponds to that commonly serving to estimate the T-wave. In some eegs the T-waves showed pronounced instability in the eegs taken before treatment with vitamin D was begun. If the T-waves are taken into account which showed the greatest deviations from normal their distribution among the cases here discussed was as follows:

Abnormal T-waves in Lead I and/or Lead II were observed in 11 (7) out of 18 cases. (Assuming that I were to have taken only one instead of three eegs in the course of the first two days of the observation time, and that I incidentally were to have made these tracings at such time as the least abnormal configurations were identifiable, the number of cases in which abnormal T-waves would have been reduced as indicated by the figures in parentheses.) Abnormal T-waves in both Leads I and II were observed in 8 (5) cases.

Abnormal T-waves in one lead were identified in 3 (3) cases.

T<sub>1</sub> was abnormal in 9 cases. In none of these cases was there evidence of a negative T<sub>1</sub>-wave. In 1 case it was diphasic, in 4 iso-electric and in another 4 it was low.

T<sub>2</sub> was abnormal in 10 cases. In 2 of them it was negative, in 4 iso-electric, and in another 4 it was low.

Out of 11 cases in which the eegs revealed abnormal T-waves 9 were examined when the serum calcium values had returned to normal. With the exception of case 10 in which the configuration of the T-wave had practically not changed, the recovery of a previously prolonged Q—T interval being in this instance the only appreciable change, the T-waves had in all cases become normal.

Out of the 7 cases in which normal T-waves were identified in the presence of hypocalcemia 4 were re-examined when the values were restored to normal. The T-waves did not show any appreciable changes.

Table 1.

*Summary Account of Significant Electrocardiographic Changes in 20 Cases of Post-Operative Hypocalcemia.*

No.	In- itials	Age	Date	Serum calcium mg%	R—R in sec.	T-waves in mm.		Q—T interval in sec.		Remarks
						Lead I	Lead II	Abs- olute	Relative <sup>1</sup>	
1 ♀	M. J.	39	8. 5.44	5.6	0.90	iso-elec- tric	negative	0.47	+ 0.11	Taken at 2 p. m.
			»		0.90	1.5	0.5	0.47	+ 0.11	Taken at 2.30 p. m.
			10. 5.44		0.90	1.5	1.0	0.48	+ 0.12	Taken at 9 a. m.
			»		0.90	1.5	iso-elec- tric	0.48	+ 0.12	Taken at 9.30 a. m.
2 ♀	E. D.	20	22. 10.45	10.6	1.10	2.0	2.5	0.42	+ 0.02	
			19. 10.45	6.7	0.80	0.5	slightly negative			
			29. 11.45	7.0	0.90	0.5	iso-elec- tric			
			»		1.10	0.5	2.0	0.51	+ 0.11	Taken after admin- istration of ergo- tamine.
3 ♀	T. J.	34	29. 12.45	10.0	0.90	1.5	1.0	0.40	+ 0.04	
			9. 12.47	7.0	0.80	0.5	0.5	0.42	+ 0.08	
			15. 6.47	5.5	0.60	iso-elec- tric	iso-elec- tric			
			»		0.70	0.5	0.5	0.38	+ 0.06	Taken after admin- istration of ergo- tamine.
			5. 7.47	16.0	0.70	iso-elec- tric	iso-elec- tric			
			»		0.75	0.5	0.5	0.32	— 0.01	Taken after admin- istration of ergo- tamine.
4 ♀	L. K.	23	19. 7.47	7.0	0.75	1.0	1.0	0.41	+ 0.08	
			7. 8.47	10.9	0.85	1.5	2.0	0.37	+ 0.02	
			25. 8.47	16.0	0.75	1.5	2.0	0.32	— 0.01	
			19. 10.46	7.3	0.85	0.5	iso-elec- tric	0.46	+ 0.11	
5 ♀	S. M.	40	24. 10.46	9.3	1.00	2.0	2.5	0.41	+ 0.03	
			17. 5.46	7.1	0.60	iso-elec- tric	0.5			
			18. 5.46		0.70	0.5	0.5			
			»		0.90	1.0	1.5	0.46	+ 0.10	Taken after admin- istration of ergo- tamine.
			23. 5.46	9.7	0.90	1.5	1.5	0.40	+ 0.04	

No.	In- itials	Age	Date	Serum calcium mg%	R—R in sec.	T-waves in mm		Q—T interval in sec.		Remarks
						Lead I	Lead II	Absol- ute	Relative <sup>1</sup>	
6 ♀	A. M.	55	28. 1.47	5.4	1.00	0.5	0.5	0.46	+ 0.08	
			29. 1.47		0.80	2.0	2.0	0.42	+ 0.08	
			2. 4.47	13.6	0.80	2.0	2.0	0.35	+ 0.01	
7 ♂	N. L.	56	9. 1.48	10.1	0.80	1.5	2.0	0.38	+ 0.04	
8 ♀	R. W.	61	1. 11.45	7.4	1.10	diphasic	4.0	0.53	+ 0.12	
			15. 9.48	4.8	0.90	2.5	1.5	0.59	+ 0.23	
			16. 9.48		0.90	1.5	iso-elec- tric	0.66	+ 0.30	
			29. 9.48	6.0	0.55	iso-elec- tric	iso-elec- tric	—	—	Taken at 8 a. m.
			"		0.85	1.5	iso-elec- tric	0.52	+ 0.17	Taken at 4.30 p. m.
			10. 10.48	9.7	0.85	1.5	1.0	0.40	+ 0.05	
9 ♀	I. W.	17	7. 12.40	5.1	0.60	1.5	< 0.5	0.42	+ 0.12	
10 ♂	R. S.	26	21. 5.46	6.9	1.05	1.0	0.5	0.46	+ 0.07	
			"		1.05	1.5	iso-elec- tric			
			27. 5.46	10.5	0.90	1.0	iso-elec- tric	0.40	+ 0.04	
11 ♀	J. P.	49	14. 10.44	6.4—7.0	0.70	1.5	2.0	0.42	+ 0.10	
			24. 10.44	9.8	0.65	2.0	2.0	0.33	+ 0.02	
12 ♀	A. S.	44	31. 6.46	7.4	0.70	2.0	2.0	0.41	+ 0.09	
13 ♀	M. S.	45	17. 1.46	6.3	0.60	1.0	1.5	0.35	+ 0.05	
			29. 1.46	10.6	0.80	1.0	1.0	0.34	± 0	
14 ♀	M. N.	35	27. 7.45	6.7	0.75	2.5	3.0	0.40	+ 0.07	
			29. 9.47	13.6	0.75	2.0	1.5	0.32	— 0.01	
15 ♀	S. W.	56	21. 2.48	7.0	1.00	2.0	2.5	0.45	+ 0.07	
16 ♀	A. P.	27	21. 1.45	7.5	0.80	2.0	4.0	0.42	+ 0.08	
			4. 3.46	14.9	0.80	2.5	2.5	0.34	± 0	
			5. 3.48	10.2	0.70	2.5	2.5	0.34	+ 0.02	
17 ♀	L. M.	36	29. 3.39	7.0	0.60	1.5	2.0	0.38	+ 0.08	
			6. 10.43	8.7	0.60	1.5	2.0	0.32	+ 0.02	
18 ♀	E. J.	53	6. 10.44		0.55	1.0	2.0	0.30	+ 0.01	Before thyroidec- tomy. Thyrotoxi- cosis.
			16. 6.45	5.6—6.3	0.70	1.0	2.0	0.44	+ 0.12	
			26. 6.45	7.0	0.65	1.0	1.5	0.44	+ 0.13	
					0.65	0.5	0.5			Taken at 8.30 a. m.
19 ♀	J. K.	25	14. 6.46	6.1	0.60	negative	negative	0.47	+ 0.17	Taken at 9.30 a. m.
			19. 9.46	6.7	0.90	0.5	iso-elec- tric	0.46	+ 0.10	Myxoedema.
20 ♀	T. F.	48	6. 3.46	7.1	1.10	low di- phasic	0.5	0.50	+ 0.10	Myxoedema

<sup>1</sup> The relative Q—T interval represents the length of the Q—T interval in relation to the average length of the normal Q—T interval as determined from the formula:  $Q-T = 0.2 R-R + 0.18$  (Ljung 1948).

### *Instability of the T-wave.*

In the first cases examined it was already noticeable that the shape of the T-wave tended to vary widely, changing under standard conditions of examination from hour to hour. The eegs of case 1 (Fig. 1) taken at half-hourly intervals revealed significant changes in the T-waves (Fig. 1 a, b). Another eeg taken two days later revealed a normal configuration (Fig. 1, c). Again another, taken half-an-hour later, showed that the T<sub>2</sub> wave was iso-electric (no treatment was given during



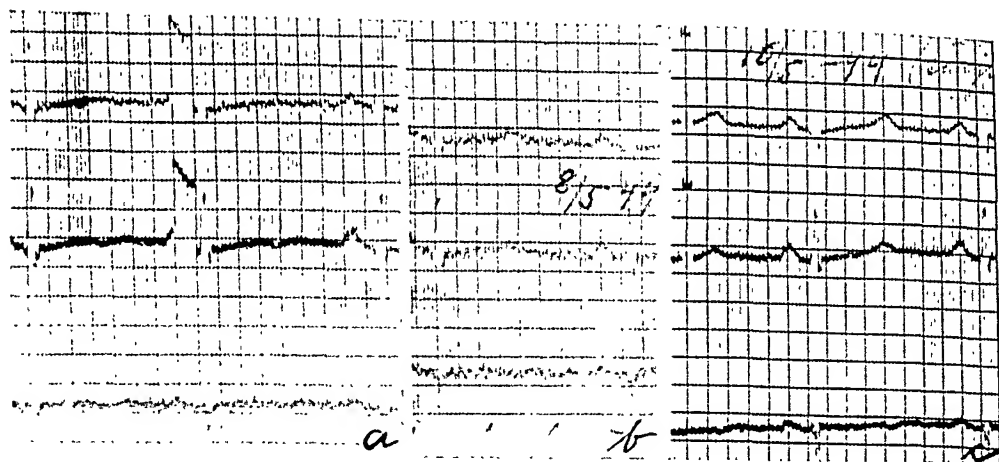


Fig. 1. *Case 1.* Post-operative hypocalcemia. Serum calcium: 5.6 mg. %. a) Ecg taken on May 8, 1944 at 2 p. m.: Cardiac rate 55;  $T_1$ -wave iso-electric;  $T_2$ -wave negative. b) Ecg taken half an hour later: Cardiac rate unchanged;  $T_1$ -wave normal;  $T_2$ -wave low positive; Q—T interval prolonged (+ 0.12 seconds). c) Ecg taken two days later; Cardiac rate unchanged;  $T_1$ - and  $T_2$ -waves normal.

the observation time). In case 18, the ecgs taken on June 26, 1945, showed that normal T-waves changed into abnormal ones during one hour. In case 6, the first ecg revealed low T-waves whereas that taken on the following day at the same hour as the preceding one, disclosed that they had become normal (Fig. 2). In case 8, the  $T_2$ -wave was on one day (Sept. 15, 1948) normal whereas on the following day it was iso-electric (Fig. 5). Again on another day (Sept. 29, 1948), the  $T_1$ -wave was alternately normal and abnormal. This case will be discussed at greater length later on in this paper.

An attempt at restoring the T-wave to normal by injecting ergotamine was made in 4 cases only. In 2 of them the abnormal T-waves became normal in response to this treatment. In case 2 the iso-electric  $T_2$ -wave became positive (Fig. 3, Ljung, 1945). In case 5, the  $T_1$ - and  $T_2$ -waves which had been abnormally low returned to

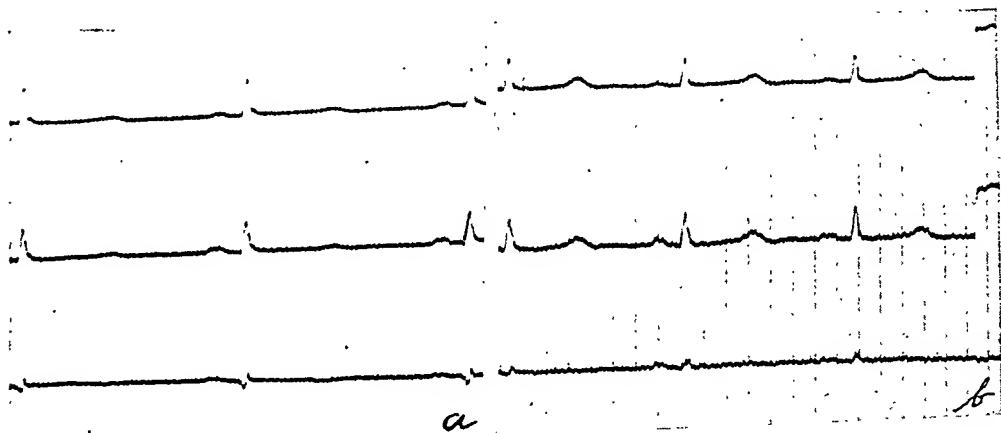


Fig. 2. *Case 6.* Post-operative hypocalcemia. Serum calcium: 5.4 mg%. a) Ecg taken on Jan. 28, 1947: Cardiac rate 60;  $T_1$ - and  $T_2$ -waves low positive. b) Ecg taken on the following day at the same hour as the preceding one: Cardiac rate 75;  $T_1$ - and  $T_2$ -waves normal.

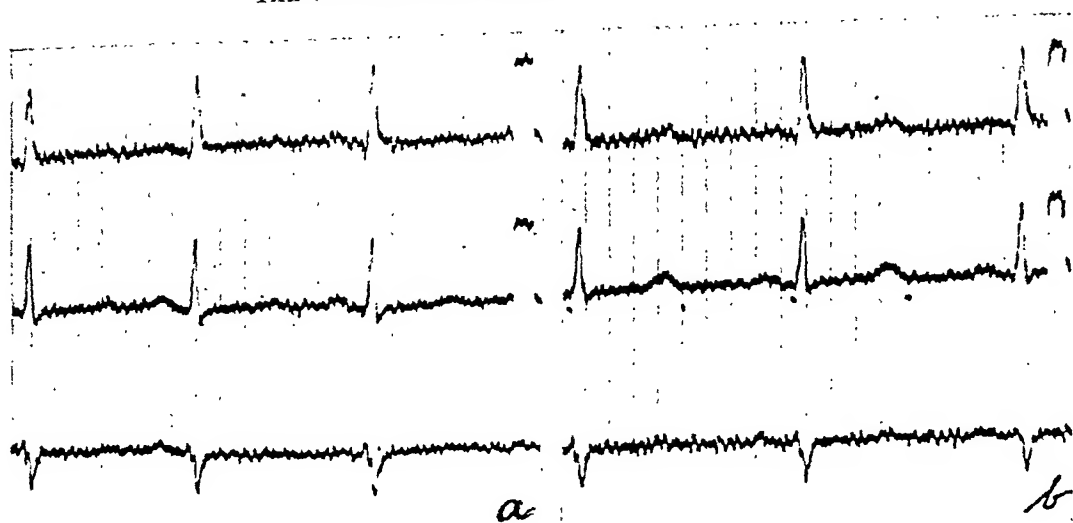


Fig. 3. Case 5. Post-operative hypocalcemia. Serum calcium: 7.3 mg%. a) Ecg showing a cardiac rate of 85; a low positive  $T_1$ - and  $T_2$ -wave. b) Ecg taken after the administration of ergotamine: Cardiac rate 67;  $T_1$ - and  $T_2$ -waves normal.

normal in response to ergotamine (Fig. 3). In case 8 there was no response to this drug. In case 3, the T-waves had before the administration of ergotamine been iso-electric (Fig. 4 a), after its administration they were just appreciable (Fig. 4 b). Another interesting observation made in this case was as follows: On July 5, 1947, the serum calcium value was 16 mg% whereas the eeg revealed iso-electric T-waves (Fig. 4 d). This configuration of the T-wave corresponded to that identified when the serum calcium was markedly reduced (Fig. 4 a). Like many other investigators I have often used the Q—T interval as control for the blood serum calcium content. The result has been that I detected errors in the laboratory findings in a few cases. To verify the diagnosis of hypercalcemia I administered to this patient  $\frac{1}{4}$  mg ergotamine by subcutaneous injection. Although no normal T-waves were identified in the eeg taken 45 minutes after the administration of this drug, low and broad T-waves were clearly seen in Leads I and II (Fig. 4 e) suggesting that the Q—T interval was not prolonged but shortened. Hence, also hypercalcemia may produce iso-electric T-waves, the «masked» Q—T interval being not prolonged but either normal or shortened. This has in the cases discussed above been evidenced by the configuration of the T-waves in response to a small dose of ergotamine. In this case it was in the first months of treatment difficult to maintain the serum blood calcium content at a normal level. Abnormally low values alternated with abnormally high ones. Another eeg taken when the serum calcium value was 16 mg% showed that the amplitude of the T-waves was normal and the Q—T interval shortened (Fig. 4 c).

#### *Appearance of the electrocardiogram after exercise.*

In 5 cases in which the T-waves were abnormal (cases 1, 2, 3, 4, 6) several eegs were taken after exercise. They did not reveal anything abnormal. None of these patients complained of cardiac pains either during or after exercise.

In case 8 there were no signs of heart insufficiency. Apart from one or two

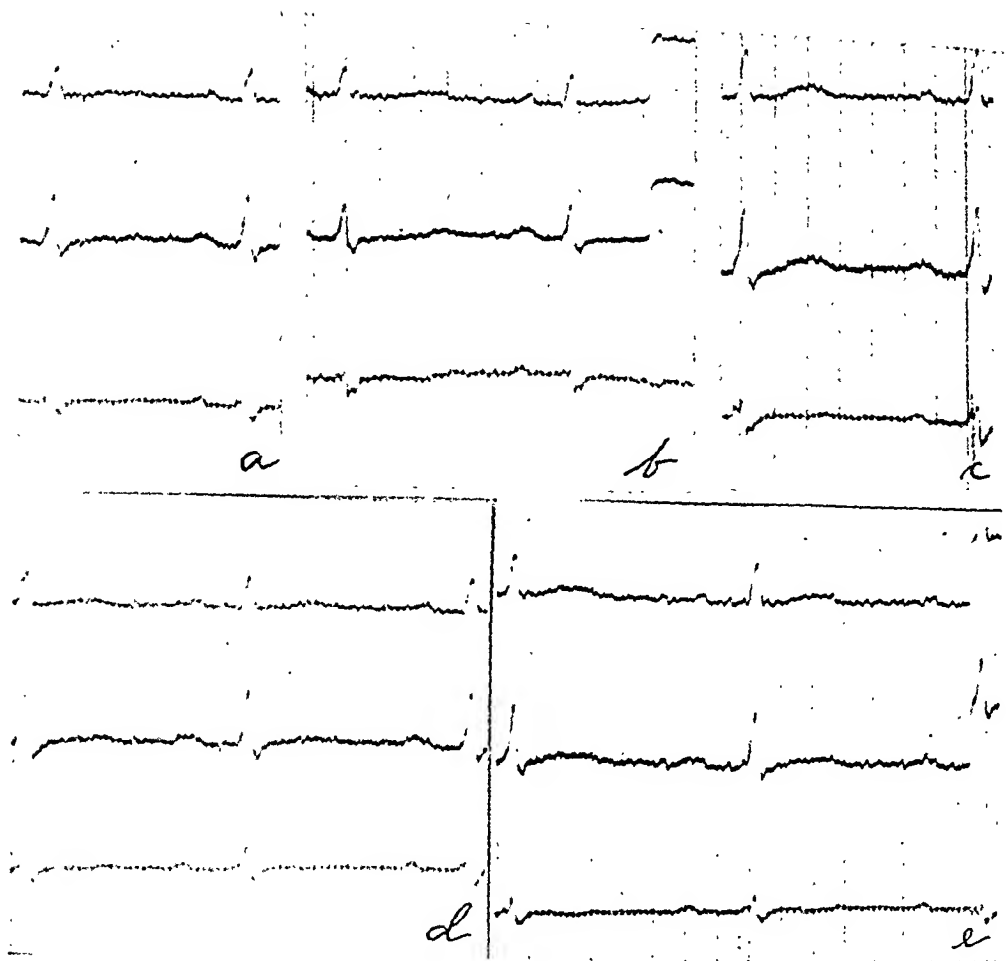


Fig. 4. Case 3. Post-operative hypocalcemia. a) Ecg taken on May 15, 1947, serum calcium being 5.5 mg%: Cardiac rate 100;  $T_1$ - and  $T_2$ -waves iso-electric. b) Ecg taken after the administration of ergotamine: Cardiac rate 85;  $T_1$ - and  $T_2$ -waves low positive. Although it was difficult to measure accurately the Q—T interval it was appreciably prolonged (about + 0.06 seconds). c) Ecg taken on Aug. 28, 1947, serum calcium being 16 mg%: Cardiac rate 80;  $T_1$ - and  $T_2$ -waves normal (slightly broader than in the presence of a normal serum calcium value); Q—T interval slightly below the average value (— 0.01 seconds). d) Ecg taken on July 5, 1947 serum calcium being 16 mg%: Cardiac 85;  $T_1$ - and  $T_2$ -waves iso-electric. e) Ecg after the administration of ergotamine: Cardiac rate 80;  $T_1$ - and  $T_2$ -waves low positive: although it was difficult to measure accurately the Q—T interval it may be seen that the «masked» Q—T interval was not prolonged as against the findings on May 15, 1947.

extrasystoles, the physical examination did not reveal anything abnormal. The blood pressure was 140/70. X-ray examination of the heart revealed a slight general enlargement (volume 490 c.c. per square meter body surface). There was no evidence of malformation. This patient was aged 61 years (she was the oldest amongst the patients here discussed). There might therefore have been some myocardial lesion though it could not be proved. The other patients did not manifest any signs of a cardiac disease. There was no history of cardiac pains comparing in type to those marking angina pectoris. Some patients complained of breast pangs and heart consciousness which are common in patients suffering from autonomic imbalance.

Table 2.

*Summary Account of Significant Electrocardiographic Changes in 8 Cases of Hypocalcemia of a Type other than Post-Operative Hypocalcemia.*

No.	In, initials	Age	Date	Serum calcium mg%	R—R in sec.	T-waves in mm		Q—T interval in sec.		Remarks
						Lead 1	Lead 2	Absolute	Relative	
21 ♂	D. J.	16	21. 5. 43		0.75	iso-elec- tric	negative			Chronic nephritis.
			26. 5. 43	4.7	0.85	0.5	1.5	0.48	+ 0.13	Taken at 8 a. m.
			8. 12. 43	6.6	0.80	iso-elec- tric	iso-elec- tric			Taken at 8.30 a. m.
			"		0.80	1.5	2.0	0.43	+ 0.09	Taken at 8.30 a. m.
			22. 6. 43	8.1	0.60	1.5	1.5	0.33	+ 0.03	
22 ♀	B. N.	20		4.4	0.50	1.5	2.0	0.36	+ 0.08	Chronic nephritis.
23 ♀	M. H.	17	31. 8. 45	5.3	0.50	1.0	1.5	0.36	+ 0.08	" "
24 ♀	E. K.	51	3. 4. 46	6.3	0.80	negative	negative	0.44	+ 0.10	" "
25 ♀	A. J.	30	1. 3. 47	5.8	0.60	1.0	1.5	0.36	+ 0.06	" "
26 ♀	N. S.	34	28. 2. 46	6.4	0.55	5.0	5.0	0.38	+ 0.09	" "
27 ♀	H. O.	52	24. 7. 45	6.7	0.55	1.5	1.0	0.35	+ 0.06	" "
28 ♂	S. W.	42	7. 5. 48	7.3	0.70	1.0	5.0	0.52	+ 0.20	Symptoms suggest- ing sprue after re- section of a large portion of the small intestine.

## II. Hypocalcemia of a type other than post-operative hypocalcemia.

All the patients of the group of chronic nephritis had a severe anemia when their eegs were taken. With the exception of cases 21 and 24 their eegs revealed a normal pattern of the QRS-complexes, S—T segments, and T-waves. The condition of these patients (case 21 excepted in which the patient had been keeping fairly well for several months) was so serious when their eegs were taken that it was not possible to study the variations in the shape of the T-waves. All died, most of them shortly after their eegs had been taken. In case 21 the patient was a boy, aged 16 years; his blood picture closely resembled that found in patients suffering from renal rachitis. He had for about three years been having slight spasms of the muscles of the fingers. His history and the findings at the examination strongly suggested that hypocalcemia due to nephritis had been present during this period of time. He was suffering from anemia and was admitted to hospital to elucidate its cause. An iso-electric  $T_1$ -wave and a negative  $T_2$ -wave (Fig. 1, Ljung, 1946) were already revealed by the first eeg, the serum calcium being at that time about 5 mg%. When the serum calcium was about 7 mg% the  $T_1$ -wave and  $T_2$ -wave were, in the morning with the patient in bed, iso-electric. The T-waves were markedly instable. The eeg taken on slight exertion, for instance, after the patient had walked at a leisurely pace from the ward to the examination room, revealed normal T-waves which remained normal for from 10 to 20 minutes. Later, they gradually became again abnormally low (Fig. 2, Ljung, 1945). The control examinations made twice or three times daily over three consecutive days revealed identical conditions. The T-waves were normal when the serum calcium

value was above 8 mg% and did not show any appreciable instability. Since no other changes were identifiable in the blood picture of this patient the assumption is warranted that the abnormal configuration of the T-waves and their instability were due to hypocalcemia (for further details see Ljung, 1946).

In case 24 the patient suffered from chronic nephritis which had long been associated with hypertension. There was also enlargement of the heart. This case does not permit of any conclusions as to the part played by hypocalcemia in producing changes in the T-waves because a myocardial lesion probably coexisted.

The Q—T interval was prolonged in all cases of chronic nephritis.

In case 28, the patient developed after resection of a large portion of the small intestine symptoms suggesting sprue. There were among other symptoms fatty stools, the patient was dehydrated, and the serum potassium content was reduced (13.4 mg%). The S—T segment was lowered in all leads and the Q—T interval markedly prolonged. Broad T-waves of about 0.30 seconds were present in all leads.

### Discussion.

A study of the type of electrocardiographic changes produced by hypocalcemia should reasonably be based on a group of cases where, apart from hypocalcemia, no other metabolic disturbances are present which may produce modifications in the eeg. Otherwise there is danger of interpreting these changes as being due to hypocalcemia. If, for instance, coma hepaticum or diabeticum, serious intestinal diseases, etc., are accompanied by a low serum calcium value, and the Q—T interval is appreciably prolonged, it should be borne in mind that the Q—T interval may in these cases be prolonged also in the absence of hypocalcemia (Hegglin, 1947). These cases therefore are not suited for a study of the effect of hypocalcemia upon the eeg.

In one case of chronic nephritis (case 21), apart from the variations in the serum blood calcium content, the variations in the other symptoms were not correlated with the changes in the tracings. The assumption is therefore justified that the latter were due to hypocalcemia. In cases of chronic nephritis, however, a marked reduction of the serum calcium content does not occur until such time as the patient develops severe uremia, *i. e.* in the final stages of nephritis. This is the reason why these cases are, as a rule, not suited for a study of the effect of hypocalcemia upon the electrocardiographic tracings.

The cases where hypocalcemia is due to hypoparathyroidism are best suited for such studies. I was not able to trace any data on the incidence of the combination of hypocalcemia and hypothyreosis. Among the 20 cases of post-operative hypocalcemia here presented there was definite evidence of hypothyreosis in 3. The possibility of this combination should always be considered when evaluating the eegs of these patients. Otherwise, abnormal configurations produced by hypothyreosis may be ascribed to hypocalcemia. This will be discussed in greater detail in another paper (Ljung, 1949).

30314.

It is at present generally accepted that a prolonged Q—T interval is pathognomonic of marked hypocalcemia. Also in the 28 cases here discussed there was evidence of a prolonged Q—T interval. Otherwise, apart from abnormally low T-waves, no changes were found in the eegs of these patients which might have been produced by hypocalcemia.

Out of the 18 cases of post-operative hypocalcemia in which hypothyreosis did not coexist abnormal T-waves were at times identified in 11. In earlier investigations a still smaller number of cases of hypocalcemia than in the present one was available for study. It is therefore not possible to assess definitely the frequency with which abnormal T-waves accompany hypocalcemia. It seems, however, that abnormal T-waves are fairly common if the blood calcium is markedly reduced.

The T-waves showed some instability when the serum calcium value was low. The variations were appreciable in eegs taken at intervals ranging between half-an-hour and two hours. In case 21 of this group of chronic nephritis the instability of the T-waves was most marked. If this patient were to have been ambulatory his eegs would always have revealed normal T-waves. If he were to have been hospitalized and kept at bed rest they would have disclosed abnormal T-waves. In the eegs of the other patients of this group there was not evidence that the T-waves tended to vary on slight exertion. In the three cases of hypocalcemia (cases 1, 18 a and 21) I studied first, the instability of the T-wave was clearly appreciable. In those studied later (cases 6 and 9 excepted in which it was again noticeable) the instability of the T-wave was not noteworthy.

Normal T-waves alternating with abnormal ones are predominantly found in patients who exhibit autonomic imbalance. As a rule, their eegs taken after exercise are normal. If any abnormal T-waves are present they become normal in response to the administration of ergotamine.

As mentioned above, eegs after exercise were taken in 5 cases of this group. They did not reveal anything abnormal. An attempt at restoring normal T-waves by the administration of ergotamine was made in 4 cases only. In 2 of them the T-waves returned to normal. The number of cases in which this drug was tested is not sufficiently large to permit of assessing its efficacy. Thus eeg in hypocalcemia seems to compare largely to that recorded in cases of autonomic imbalance. This question needs further study.

With the exception of one case the abnormal T-waves returned to normal as the serum calcium values became normal. This observation strongly suggests that the abnormal T-waves were actually produced by hypocalcemia.

It is difficult to understand why some authors ascribe abnormal T-waves recorded in the presence of hypocalcemia to a myocardial lesion. Marzahn (1934, 1935) suggested that a myocardial lesion caused by anoxemia which is brought about by the accumulation of »Ermüdungsstoffen» (owing to a prolonged systole and a shortened diastole) was responsible for the abnormal T-waves in hypocalcemia. It is difficult to believe, however, that symptoms produced by a myocardial lesion show from one day to the other such great variations as have in this study been observed in the T-waves. Moreover, it is most unlikely that these

abnormal configurations will disappear in response to vitamin D treatment. Against this background the assumption of the presence of a serious myocardial lesion seems to be ill founded.

The commonest heart symptoms accompanying hypocalcemia compare to those characterising cardiac neurosis (Lachman, 1941). In some cases, however, they resemble those marking angina pectoris. In the latter case they disappear when the serum calcium content is restored to normal. Spasms of the coronary arteries may account for these symptoms. Hoesch (1939) wrote that patients with tetany show a tendency to arterial spasms. Convincing evidence, however, that the abnormal T-waves are produced by a physio-pathologic coronary insufficiency has not yet been offered.

It is generally accepted that hypocalcemia alone does not cause heart insufficiency. Hegglin (1939), however, feels that in patients suffering from a heart lesion of other origin hypocalcemia is a contributory factor in heart insufficiency. Only in a few cases of the series here presented was there a history of heart symptoms. They compared in type to those produced by cardiac neurosis.

It has been reported that the T-waves are, as a rule, of normal breadth in hypocalcemia, the Q—T prolongation being brought about by the prolongation of the S—T segment. According to White (1945) the values of a normally broad T-wave vary between approximately 0.10 and 0.25 seconds. If the prolongation of the Q—T interval is due to other causes (as a rule, a serious metabolic disturbance is responsible for it) the T-waves are often abnormally broad. This is illustrated by case 28. In an earlier paper (Ljung, 1948) I have pointed out that it is in these cases not possible to draw any conclusions as to the part played by the blood calcium serum content in producing say prolongation of the Q—T interval because the latter may be markedly prolonged also in cases where the serum calcium values are normal. With the exception of one case (case 8) where the breadth of the T-wave deviated from normal in one tracing, they were in the cases of post-operative hypocalcemia here discussed of normal breadth. On Oct. 15, 1948, the breadth of the T<sub>1</sub>-wave was in this case 0.23 seconds. On the following day it increased to 0.30 seconds, the heart rate having been the same. The Q—T interval was lengthened in a corresponding degree from 0.59 to 0.66 seconds (Fig. 5 a and b). The phonocardiogram showed that the mechanical systole (measured from Q to the beginning of the second heart sound) was on both occasions about 0.46 seconds. In subsequent eegs, the T-waves were of normal breadth.

In case 3 both hypocalcemia and hypercalcemia produced iso-electric T-waves which returned to normal when the serum calcium values became normal.

The observations made in cases 3 and 8 further illustrate that, at the present state of our knowledge, it is very difficult to explain the factors concerned in producing abnormal T-waves as well as their significance in the presence of hypocalcemia.

The factors producing abnormal T-waves in hypocalcemia are still undetermined. Convincing evidence that they are caused by a serious myocardial lesion or a physio-pathologic insufficiency of the coronary arteries has hitherto not been furnished. The most attractive hypothesis is that a functional disturbance of the

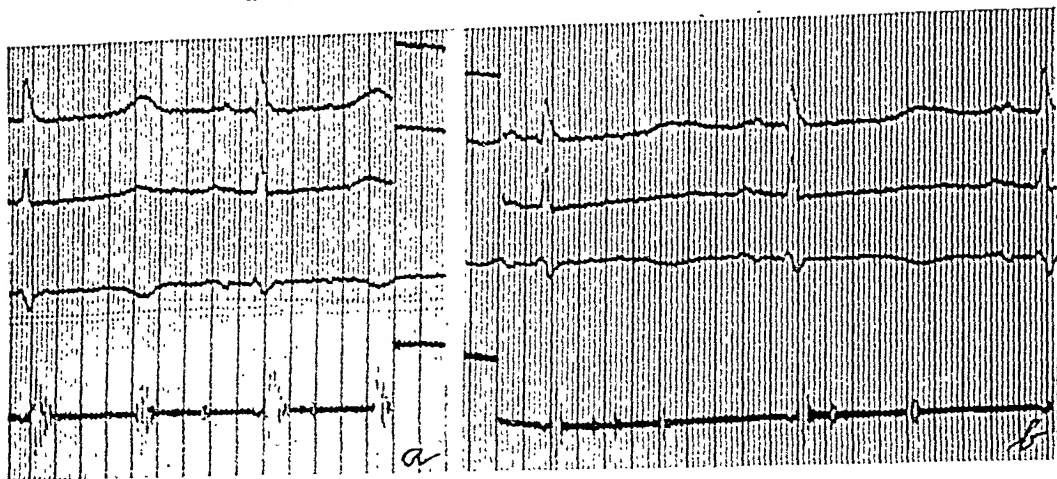


Fig. 5. *Case 8.* Post-operative hypocalcemia. a) Ecg taken on Sept. 15, 1948, serum calcium being 4.8 mg%: Cardiac rate 67; normal  $T_1$ - and  $T_2$ -waves and a markedly prolonged Q—T interval (+ 0.23 seconds). b) Ecg taken on the following day: Cardiac rate unchanged;  $T_1$ -wave slightly lower than on the preceding day and abnormally broad;  $T_2$ -wave iso-electric;  $T_3$ -wave broader than in the preceding ecg; Q—T interval still more prolonged (+ 0.30 seconds).

myocardium is responsible for the abnormal pattern of the T-waves in the presence of hypocalcemia.

### Summary.

Report of 28 cases of hypocalcemia. All patients had on one occasion a blood serum calcium value of or below 7.5 mg%. In 20 of them post-operative hypocalcemia was present. It is stated that these cases are best suited for a study of the effect of hypocalcemia upon the electrocardiogram.

The Q—T interval was prolonged in all cases. Out of 18 cases of post-operative hypocalcemia abnormal T-waves in Leads I and/or II were at times recorded in 11. Their significance is discussed.

As the blood serum calcium values returned to normal (in response to vitamin D treatment) the Q—T interval and the T-waves became as a rule normal. Apart from the changes mentioned above nothing abnormal was identifiable in the electrocardiograms studied.

### References.

- Aschenbrenner, R. & Bamberger, Ph.: *Klin. Wschr.* 1935, 14, 1494. — Barker, P., Johnston, F. & Wilson, F.: *Amer. Heart Journ.* 1937, 14, 82. — Carter, E. P. & Andrus, C.: *Journ. Am. Med. Ass.* 1922, 78, 1922. — Cellina, M. & Selvini, A.: *Fol. Card.* 1946, 5, 77. — Doxiades, L. & Vollmer, H.: *Klin. Wschr.* 1927, 6, 1801. — Fernbach, J. & Szandany, Z.: *Klin. Wschr.* 1940, 19, 372. — Hecht, H. & Korth, C.: *Zschr. Kreislaufforsch.* 1937, 29, 577. — Hegglin, R.: *Helvet. Med. Act.* 1939, 6, 584. — Hegglin, R.: *Bibliotheca Card. Fasc. II*, 1947. — Hegglin, R. & Holzmann, M.: *Zschr. Klin. Med.* 1937, 132, 1. — Hoesch, K.: *Nord. Med.* 1939, 1, 762. — Jores, A.: *Klinische Endokrinologie*. Berlin 1942. — Justin-Besançon, L. & Laroche, Cl.: *Ann. Endocrin.* 1943, 4, 213. — Lachman, A.: *Acta Med. Scand.* 1941, Suppl. 121. — Ljung, O.: *Nord. Med.* 1945, 27, 1925. — Ljung, O.: *Acta Med. Scand.* 1946, 124, 38. — Ljung, O.: *Sv. Läk. Tidn.* 1948,



2125. — Ljung, O.: *Acta Endocrin. Scand.* 1949, in press. — Mannheimer, E.: *Nord. Med.* 1939, 1, 613. — Marzahn, H.: *Zschr. Klin. Med.* 1934, 127, 182. — Marzahn, H.: *Deutsch. Med. Wschr.* 1936, 61, 507. — Migliori, V.: *Bull. Sci. Med.* 1938, 110, 94. — Morgenstern, K.: *Zschr. Kinderheilkunde* 1914, 11, 304. — Nadrai-Pecz, A.: *Erg. inn. Med. u. Kinderheilk.* 1941, 60, 688. — Rasmussen, H.: *Klinisk Elektrokardiografi.* Oslo 1946. — Scherf, D. & Boyd, L. J.: *Clinical Electrocardiography.* London 1945. — Schiff, Er.: *Acta Paed.* 1923—24, 3, 57. — White, P. D.: *Heart Disease.* New York 1945.

---

## Nekrotisierende Jejunitis.

Von

Dr. med. habil. GUNNAR BERG.

Chefarzt Krankenhaus Borstel über Bad Oldesloe (Deutschland).

(Bei der Redaktion am 12. Februar 1949 eingegangen.)

Als im Sommer 1946 — in den ersten Junitagen — in einem Lager N. in Holstein gehäuft Gastroenteritiden auftraten, so hat das die diensttuenden Aerzte natuerlich wenig ueberrascht. Anlass zu irgendwelcher Besorgnis bestand zunaechst auch nicht, da die ersten Faelle sehr leicht mit wenigen Stuhlentleerungen, mehrmaligem Erbrechen und relativ rascher Erholung verliefen. Solche Erscheinungen sind ja bei Menschengruppen, die dicht zusammenleben und aus grossen Gemeinschaftskuechen gespeist werden, keine Seltenheit. In unserem Lager waren Maenner untergebracht, die von der Aussenwelt isoliert waren. Die Ernaehrung entsprach etwa derjenigen der Bevoelkerung jener Gegend. Ich erlebte diese Krankheitserscheinungen als Revierarzt, der zugleich die ambulanten Kranken zu betreuen hatte und konnte so — unter den gleichen Bedigungen wie die Kameraden lebend — das Auftreten der Massenerkrankung genau studieren. So hatte ich Gelegenheit auch all die leichten Faelle zu beobachten und zu behandeln, die der im Krankenhaus taetige Arzt nicht zu sehen bekommt.

Stuetzig wurden wir Aerzte erst, als die Krankenzahl rasch stieg und Symptome auftraten, die wir bei den Sommerdurchfaellen nicht zu sehen gewohnt waren. Die Krankheit setzte immer ein mit Durchfaellen, die nicht besonders heftig waren und meist nach weniger Tagen aufhoerten ohne den Appetit wesentlich zu beeintraehtigen. Die Stuehle — etwa 3—6 pro Tag — waren duennflussig, gefaerbt, uebelriechend, zum Teil blutig, wenig Schleim, kein Eiter; dazu starker Meteorismus, wenig Schmerzen, kaum Tenesmen. Ein eigentliches Krankheitsgefuehl wurde in diesem Stadium nicht angegeben, oder wenigstens nur selten. Viele Kranke suchten deshalb den Arzt gar nicht auf. Als wir anfangen, die Temperatur zu kontrollieren, zeigten sich subfebrile Werte, selten bis 38.5°, meist nur 37.5°. Nach einigen Tagen — der Durchfall hatte meist schon aufgehoeert — klagten die Kranken ploetzlich ueber schwerste geradezu kolikartige Schmerzen, die meist im Oberbauch und besonders auch links vom Nabel lokalisiert wurden. Jede Nahrungsauf-

Tabelle 1. (Lager N.)

Nr.	Zeit: 1946	BSG	Schmerz	Diarrhoe	Brechen	Temp.	Bemerkungen
15	24. 6.—13. 7.	25/58	++	++	0	37.5	Gr. Leber, Neurasthenie
23	29. 6.—18. 7.	20/50	++	+	0	38.2	Gr. Leber, Neurasthenie
24	1. 7.—22. 7.	32/63	++	++	0	38.2	Gr. Leber, Ulcus duodeni
29	7. 7.—13. 7.	19/42	++	++	0	37.3	
30	7. 7.—15. 7.	16/34	++	++	0	37.0	Groesse: 186 cm/69 kg
31	8. 7.—20. 7.	20/43	++	++	0	37.8	Gr. Leber. Erhielt 6 g Eubasin
49	16. 7.—22. 7.	42/73	+	++	0	36.7	
50	22. 7.— 5. 8.	50/72	++	+++	0	38.0	Oedeme
52	23. 7.— 3. 8.	12/26	++++	++	+	37.1	Gr. Leber, 7 g Eubasin i. m.
53	24. 7.—14. 8.	25/50	++++	++	+	37.8	Oedeme
62	4. 8.—18. 8.	16/40	++	+++++	0	37.2	Gr. Leber, nerv. Magenleiden
66	13. 8.—21. 8.	15/42	++	+++	0	37.6	Guter E. Z.
70	17. 8.— 9. 9.	40/83	+	++	+++	38.1	Gleichzeitig Lumbago
74	26. 8.—13. 9.	11/31	++	+	0	37.9	Gr. Leber
76	30. 8.—23. 9.	38/65	++++	++	+	39.1	Gr. Leber, Stomatitis
77	4. 9.—18. 9.	47/75	++	+++	0	38.5	Gr. Leber

nahme, ja schon ein Schluck Tee oder eine Kohlekomprette konnte den Schmerz aufs heftigste steigern, ebenso verschlimmernd wirkten Kaelte oder Bewegungen. Jeder Appetit hoerte auf. Brechneigung plagte den Kranken, der ganz seinem Schmerz hingegeben dalag. Guenstig wirkten absolute Ruhe und Waerme unter Vermeidung von Druck auf den Leib. Atropin half fast gar nicht oder erst beim Abklingen der Schmerzen, was nach etwa 3 Tagen begann. Im Schmerzstadium absolute Stuhltraegheit, weisse, trockne Zunge. Fluessigkeit konnte nur unter Umgehung des Magens zugefuehrt werden. Die Kranken verloren sehr stark an Gewicht. Langsam wurden die Schmerzen geringer, allmaechlich konnte der Kranke essen, zurnechst noch mit Schmerzen, bald wurde er frei und entwickelte nun einen riesigen Appetit. Stuhlgang war zunaechst nur mit Einlaeufer zu gewinnen, dann wurde er normal. Die Revierkranken brauchten meist 3—4 Wochen bis zur Wiederherstellung, wenn keine Komplikationen oder Rueckfaelle auftraten wie Tab. 1. zeigt. Die Blutsenkung war oft erstaunlich hoch und ging erst nach mehreren Wochen zur Norm zurueck. Der Leib war im Schmerzanfall gespannt und im Oberbauch und um den Nabel besonders druckempfindlich. Oft fuerchtete man eine Magen- oder Darmperforation. In einigen Faellen wurden die Erscheinungen so schwer, dass eine Ueberfuehrung ins Hospital erfolgen musste, wo sich der Chirurg zur Laparotomie entschloss, da befuerchtet werden musste, dass eine Perforation, eine Pancreasnekrose oder ein Ileus im Entstehen waren. In drei Faellen — bei vielen Hunderten, vielleicht sogar einigen Tausenden von Erkrankten — wurde der Bauch geoeffnet. Es zeigte sich nun bei allen drei Operierten, dass das Jejunum in ganzer Ausdehnung hochgradig geschwollen und geroetet war, die Serosa wies Blutungen auf, in der Bauchhoehle war etwas blutiges Exsudat. In einem Falle war die Entzuendung bis zur Nekrose fortgeschritten, ein Stueck des Jejunum musste reseziert werden. Auch in der Schleimhaut fanden sich nun ausgedehnte Blutungen. Die Untersuchung ergab das Bild einer schweren haemorrhagischen Jejunitis mit Nekrosen. Ein Kranker starb. Untersuchungen von Blut und Stuhl auf Erreger und Agglutination blieben negativ. — In einigen Teilen des Lagers



Tabelle 2. (Lager E.)

Nr.	Zeit	BSG	Temp.	Leuco- cyten	Sacure	mm Hg	Bemerkungen
78	9. 12. 46	26/38	37.5	10,700			1942 Hepatitis BSG nach 1 Woche: 25/51 Appendektomie 25. 12. 46 Ulcus duodeni seit 1941
79		55/77	—	12,200			
80	1. 1.—18. 2.	45/61	—	—		120/75 135/85	
81		24/45	—	16,000			
	3. 1.—Febr.	60/97		10,100			
		9/21		7,300			
82	3. 1.—17. 2.	65/90		5,800		100/65 120/75	Chron. Gastritis seit 19 J. Ulc. duodeni seit 20 J. 1933 und 1942 Magenop., zum Schluss Resektion. seit 1942 Gallenleiden
83		35/35		6,900			
	8. 1.—10. 2.	15/32		13,500		110/70	
		7/20					
84	21. 1.—17. 2.	69/97	38.7	17,800	13/21	80/50	seit 1938 Ulcus duodeni Duodenalsaft steril
85		19/55					
	23. 1.—10. 2.	43/65	37.6	11,000	9/17	105/70	
		17/38		7,300			
86	28. 1.—14. 2.	17/28		15,500			
		38/49		10,200			
	Januar 47	20/45	37.4	12,750	33/43	110/75	seit 1936 Ulcus ventric.
		19/41					
87	Januar 47	48/104		13,600			seit 1936 Ulc. duodeni Bulbusdeformierung
		47/70					
89	Januar 47	21/59	37.7	18,300	anacid		seit 1926 Ulc. ventr. 1932 Ulcusblutung
		14/27					
90	Januar 47	52/73	37.3	26,500			
		27/50					
91	Januar 47	28/54	38.5	16,400			
		6/18					
92	Januar 47	97/112	38.7	25,900			7. 1. Probelap.: Jejunitis
		7/41					
93	Januar 47	53/95		15,800			5. 1. Probelap.: Jejunitis. Duode- nalsaft steril
		23/49					
	Januar 47	13/35		12,500			
		—					
94	7. 1. 47	17/40					
		25/41					
95	5. 1. 47	—					
		21/47					

Wenn bei BSG, Leucocyten und Blutdruck mehrere Zahlen bei einem Kranken angegeben sind, sind die Werte meist je eine Woche nacheinander gewonnen.

jedoch im Stadium des Heisshungers rasch wieder aufgeholt. Sicher handelte es sich zum Teil um Verlust und Wiederaufnahme von Wasser.

Die Therapie bestand anfangs in erster Linie in totaler Ruhigstellung, Enthaltung von Essen und Trinken, Vermeidung oraler Arzneigabe. Kamen die Kranken sehr frueh, was fast nie der Fall war, wurde Reinigung von Magendarmkanal durch Magen- und Darmspuelung angestrebt. Wichtig erschien Waerme, Sicherung des Schlafes (Luminal subkutan) und der Fluessigkeitszufuhr (per Klysma oder i. v.). Da Atropin wenigstens anfangs zur Schmerzbekaempfung absolut nicht ausreichte, gaben wir Dolantin, jedoch sparsam. Vielleicht koennte man auch Novalgin i. v. geben. Sulfonamide steigerten selbst bei intravenoeser Zufuehrung meist den Brechreiz so stark, dass wir spaeter ganz darauf verzichteten. Nach Ueberwindung des akuten Stadiums gaben wir zunaechst kleine Mengen Tee, dann Schleim und Brei. In dieser Zeit war etwas Atropin nach dem Essen angebracht, um die Angst

vor den Schmerzen nach dem Essen zu nehmen. Ist der Schmerz einmal vorueber, dann muss man mit der Steigerung der Nahrungszufuhr sehr vorsichtig sein, da die Rekonvaleszenten im Heisshunger ueber jedes vertraegliche Mass hinaus zu essen verlangen.

Soweit hatte ich 1947 meine Beobachtungen niedergeschrieben, ohne etwas von dem zu erfahren, was in unserer Umwelt inzwischen geschehen war. Dann erst bekam ich Kenntniss von den Erfahrungen, die vorwiegend in Hamburg und Luebeck mit der gleichen Krankheit gemacht worden waren, die in Luebeck als »Darmbrand«, in Hamburg als »nekrotisierende Enteritis« und bei uns im Lager als »Jejunitis« bezeichnet wurde, da im klinischen Bild der Schmerz im linken Oberbauch in erster Linie auf das Jejunum hinweist.

Soviel ich sehe, haben v. Falkenhausen und Gaida (7) in Hamburg (abgesehen von Einzelfaellen aus aelterer Zeit, wie sie Hormann (14) zusammengestellt hat) zuerst das klinische Bild der nekrotisierenden, phlegmonoes-haemorrhagischen Enteritis vor allem des Duodenums und Jejunums dargestellt im Zusammenhang mit den Folgen chronischer Unterernaehrung. Bei den wissenschaftlichen Tagungen in Hamburg (November und Dezember 1946, April und Oktober 1947) und Luebeck (Juli 1947 und Juni 1948) wurde das Bild von den verschiedenen Fachvertretern geschildert. Neben den Internisten und Chirurgen kamen Roentgenologen und Pathologen zum Wort.

Die pathologisch-anatomischen Befunde wurden besonders dargelegt von Heine (13) in Hamburg (Dez. 1946), von Griesmann (12) auf der Tagung der Nordwestdeutschen Gesellschaft fuer Innere Medizin in Hamburg (Maerz 47) und Siegmund in Muenster und Duesseldorf (Juli 1947).

Die Ergebnisse der Roentgenuntersuchung mit und ohne Kontrastmittel teilten mit Kruse in Hamburg (21), Fehlhaber in Duisburg (9), sowie Kruse, Frick und Vatter (22) beim Roentgenologentreffen in Bevensen (Mai 47). Vor Kontrastdarstellung im akuten Stadium muss nach den gemachten Erfahrungen unbedingt gewarnt werden. Neu duerfte die Tatsache sein, dass auch in Skandinavien Faelle von »Jejunitis acuta phlegmonosa« in der Gegenwart beobachtet wurden (Husebye) (16).

Angesichts dieser zahlreichen Veroeffentlichungen erschien es mir zunaechst als ueberfluessig, die in den Lagern gemachten Beobachtungen mitzuteilen. Das klinische Bild, der Verlauf, die anatomischen Befunde bei Operation und Sektion, die Komplikationen (Ileus, Perforation) und die Spaetfolgen stimmten vollkommen mit dem ueberein, was wir gesehen haben. Voellig ungeklaert bleibt jedoch die *Actiologie*. Und in dieser Hinsicht koennen unsere Erfahrungen doch vielleicht einen kleinen Beitrag zur Aufklaerung liefern.

Lippelt (15) fand ein *Bact. coli haemol.*, das bei Tieren Jejunitis hervorrief.

Schuetz (15) und Lezius (15) trafen im Jejunum von Kranken und Verstorbenen einen Anaerobier aehnlich dem Fraenkel'schen Gasbrandbacillus, der bei Tieren einen »Darmbrand« hervorrief. Dementsprechend behandelten sie mit Marbadal, sie nahmen an, dass die Erreger entweder mit der Nahrung zugefuehrt werden oder vom Dickdarm aufsteigen. Andere glaubten die Ursache in einem unbekannten Virus oder als Folge einseitiger Ernaehrung suchen zu muessen. Kulpe (Berlin)



reste erkrankten und sodann die Beobachtung zur Weihnachtszeit 1946, als nur diejenigen erkrankten, die aus der Lagerkueche gespeist wurden, während die Patienten des Hospitals, die ihr Essen aus der Kueche des Krankenhauses bekamen, verschont blieben. Nach der Beobachtung an der Dreiergruppe ist auf eine Inkubation von Stunden zu schliessen.

Schliesslich muss ich noch auf eine Beobachtung hinweisen, die von den bisher mitgeteilten abweicht: die Letalität war bei uns trotz ausgesprochener Mangelkost nicht hoch im Gegensatz zu den Mitteilungen aus Hamburg und Luebeck (40—50 %). Im Lager sahen wir eben die uebergrosse Zahl von leichten Erkrankungen, die zumeist ohne aertzliche Hilfe abklangen, während in den Staedten nur die schweren und komplizierten Faelle in die Krankenhaeuser und somit vor das Auge des berichtenden Arztes kamen. Die Praktiker duerften die zahlreichen leichten Erkrankungen als Enteritis oder leichte Nahrungsmittelvergiftung gedeutet haben, während sie die bedrohlichen Faelle als »Appendicitis, Ileus, Peritonitis, Pankreatitis«, usw. in die Kliniken einwiesen.

### Summary.

A report of accumulated cases of jejunitis in civil internment camps during the summer of 1946 and the winter of 1946—47. Contrary to earlier accounts of this disease but slight letality is shown, most probably below 2 %. In agreement with Kulpe (23) an intestinal intoxication is assumed, very likely owing to toxines occurring in food rich in carbohydrates. Incubation time: a few hours.

### Literaturverzeichnis.

1. Arlart und Schönlebe, D. M. Wschr. 1948, S. 56. — 2. Beckermann und Laas, Ärtzl. Wschr. 1946, S. 329. — 3. Dammermann, Ärtzl. Wschr. 1947, S. 481. — 4. Edelhof, D. M. Wschr. 1947, S. 228. — 5. Ernst, D. Gesdh. Wesen 1948, S. 262. — 6. v. Falkenhausen, Med. Klin. 1947, S. 385. — 7. v. Falkenhausen und Gaida, D. M. Wschr. 1947, S. 30. — 8. v. Falkenhausen, Bertram, Heine, Menzel, Kessler und Nauck, Klin. Wschr. 1947, S. 318. — 9. Fehlhaber, M. klin. 1948, S. 60. — 10. Frick, D. M. Wschr. 1947, S. 164. — 11. Fromme und v. Zimmermann, Ärtzl. Wschr. 1946, S. 233. — 12. Griessmann, Nordwestd. Ges. f. i. Med. 29.—31. Mai 1947. — 13. Heine, Ärtzl. Wschr. 1947, S. 796. — 14. Hormann, Ärtzl. Wschr. 1947, S. 998. — 15. Hormann, Jeckeln, Schütz, Letzius, Baniecki, Lippelt und Konjetzny, Klin. Wschr. 1948 S. 319. — 16. Husebye, Acta radiol. 1948, S. 71. — 17. Jeckeln, D. M. Wschr. 1947, S. 105. — 18. Jochims, D. M. Wschr. 1947, S. 166. — 19. Klinger, Chirurg 1946, S. 139. — 20. Kloos, Ärtzl. Wschr. 1947, S. 294 und 1029. — 21. Kruse, D. M. Wschr. 1947, S. 617 und 796. — 22. Kruse, Frick und Vatter, D. M. Wschr. 1948, S. 139. — 23. Kulpe, D. Gesdh. Wesen 1948, S. 268. — 24. Menzel und Boving, Ärtzl. Wschr. 1947, S. 421. — 25. Meyer-Burgdorf, D. M. Wschr. 1947, S. 186. — 26. Ruppert, D. M. Wschr. 1947, S. 108. — 27. Schütz, Letzius und Jeckeln, D. M. Wschr. 1948, S. 177. — 28. Siegmund, Klin. Wschr. 1948, S. 224. — 29. Siegmund, Med. Klin. 1948, S. 213. — 30. Wiegand, Z. ges. Inn. Med. 1947, S. 570. — 31. Wilker, Ärtzl. Wschr. 1947, S. 795.





Du Service de Gastro-Entérologie de l'Hôtel-Dieu et du Centre de Recherches de l'Hôpital Foch, Paris.

## Études des troubles du métabolisme des hydrates de carbone au cours des diarrhées chroniques dites banales.

Par

S. BONFILS et A. LAMBLING.<sup>1</sup>

(Ce travail est parvenu à la rédaction le 12 Février 1949.)

L'importance de l'étude du retentissement nutritionnel des diarrhées apparaît, sous l'impulsion de nombreux travaux, chaque jour plus considérable.

Sans aborder le problème de l'apparition primitive ou secondaire de ces troubles, problème difficilement soluble car il comporte une expérimentation animale dont les conclusions sont loin d'être toujours applicables à l'homme, les recherches récentes ont montré que ce retentissement nutritionnel est capable de toucher la quasi totalité des métabolismes de l'économie: lipides, protides, glucides, vitamines, hormones, sels minéraux en particulier.

La découverte par Thayssen (34), en 1926, des «courbes glycémiques basses» au cours des affections qu'il fait entrer dans le cadre des stéatorrhées idiopathiques — sprue tropicale ou non tropicale, maladie coeliaque — représenta le premier fait précis connu dans cet ordre d'idée.

Les recherches s'orientèrent alors presque exclusivement vers l'étude de ces stéatorrhées. Sous l'angle clinique, les travaux de Thayssen furent confirmés et précisés par de nombreux auteurs: Martin et Sciclounoff (23), Baixas (2), Turpin (35) et ses élèves, Adlersberg (1). De plus, Chesnay et McCord (13), en 1934, mirent en évidence la non-absorption de la vitamine A par la muqueuse intestinale, trouble qu'ils considèrent comme plus spécifique encore que la stéatorrhée.

D'autre part, une analyse plus strictement biologique de ces faits permit à Verzar (36) et Laszt d'obtenir, au moyen d'une intoxication chronique par l'acide mono-iodacétique, une véritable maladie coeliaque expérimentale du rat, caractérisée par des selles abondantes et grasses, une intumescence du ventre, de l'anémie, un arrêt de la croissance, de la dermatite, de l'hypophosphatémie avec ostéoporose et une glycémie basse.

Pour Verzar et ses collaborateurs, en effet, l'absorption intestinale ne suit qu'à l'égard d'un très petit nombre de substances les lois de l'osmose. Au contraire, une réaction de phosphorylation à l'intérieur de la cellule intestinale, serait obli-

<sup>1</sup> 20, Rue Greuze, Paris 16:e.

gatoire pour permettre l'absorption active du glucose, du galactose ou des glycérols nés des graisses dédoublées.

C'est ce chaînon essentiel du processus d'absorption qu'inhibe l'acide mono-iodacétique et dont l'absence permet ainsi la reproduction expérimentale des stéatorrhées idiopathiques.

Tel est le premier groupe de diarrhée où furent étudiés les troubles métaboliques et plus particulièrement celui du glucose.

Mais, bientôt, de nouveaux travaux vinrent montrer que ces faits n'étaient pas l'apanage de troubles exceptionnels, mais pouvaient survenir au cours de tous les types de diarrhée sans que, pour autant, l'interprétation en demeure, bien au contraire, plus facile.

C'est ainsi que Martin et Sciclounoff (23), Baixas (2), Adlersberg et Sobotka (1), Bercowitz et Page (3) soulignèrent tour à tour les altérations des métabolismes des hydrates de carbone, des lipides, de certaines vitamines au cours de différents états pathologiques ayant la diarrhée chronique comme symptôme commun, la majorité de ces auteurs désignant les troubles de l'absorption intestinale comme le grand coupable de ces perturbations.

Une dernière donnée, enfin, de ce problème très général a été apportée récemment par l'utilisation de l'acide folique (acide ptéroylglutamique) qui s'est montré capable d'améliorer, en un temps assez bref mais dans les seules stéatorrhées idiopathiques, ces troubles nutritionnels qui semblaient particulièrement rebelles, même au cours des périodes d'accalmie de la maladie. Ce sont de tels faits que rapportent les études de Darby, Jones et Johnson (14), Darby, Kaser et Jones (15).

Le présent travail a pour but d'étudier les troubles du métabolisme des glucides au cours des diarrhées chroniques, que nous appellerons « banales » pour les opposer au groupe des stéatorrhées idiopathiques, d'une manière aussi complète que possible par l'étude de l'épreuve d'hyperglycémie provoquée per os et par voie intraveineuse, par la mesure de l'absorption intestinale des sucres à l'aide de la sonde de Miller-Abott, enfin par le dosage sanguin de l'acide pyruvique qui, bien que plaque tournante de nombreux métabolismes, apparaît avant tout comme un stade obligatoire dans la transformation des hydrates de carbone.

Nous tenterons également d'interpréter les résultats obtenus en les comparant aux données fournies par l'étude des stéatorrhées idiopathiques pour montrer ce qui sépare et ce qui rapproche les troubles métaboliques de ces affections exceptionnelles de ceux des diarrhées banales.

## I. Étude du métabolisme glucidique.

### A. L'épreuve d'hyperglycémie provoquée per os.

Cette épreuve est à la fois très complexe et apparemment très peu spécifique puisqu'elle met en jeu successivement le transit digestif, l'absorption intestinale, la glycorégulation, fonction elle-même de l'intervention du foie, du pancréas, du système nerveux et des glandes vasculaires, sanguines, enfin de l'utilisation tis-

sulaire. C'est elle néanmoins qui a mis, il y a 20 ans, Thayssen sur la voie des troubles métaboliques et on verra plus loin que ses réponses demeurent toujours non seulement utilisables mais instructives.

*Technique.* Nous avons employé la technique la plus classique, telle qu'elle a été définie par M. Labbé: ingestion, après une première glycémie à jeun, de 50 g de glucose en solution dans 100 g d'eau. Les prélèvements sanguins, veineux ou capillaires selon les cas, en vue de dosage sont faits ensuite de 30 en 30 minutes pendant 2 h. 30.

L'épreuve a été pratiquée chez 16 sujets diarrhéiques et chez 7 sujets non diarrhéiques atteints d'affections bénignes en général, non susceptibles d'altérer l'épreuve, et destinés à servir de témoins.

*Résultats.* Dans le groupe témoin (tableau I, courbe A), les résultats sont homogènes: la flèche d'hyperglycémie est obtenue entre la 30ème et la 60ème minute et oscille entre 40 et 67 avec une moyenne de 46, les chiffres étant exprimés en mg de glucose pour cent.

Ces données sont entièrement conformes à celles qui ont été observées par de nombreux auteurs, dans les mêmes conditions, tels Labbé, Fiessinger, Boulin, mais inférieures aux constatations de Thayssen (34), qui admet que la flèche normale doit être de 70 à 100 mg.

Dans le groupe des sujets diarrhéiques, au contraire, les résultats peuvent être classés en deux séries, selon qu'ils appartiennent au type des «courbes plates» ou non; les «courbes glycémiques basses», nous l'avons vu, ont été décrites pour la première fois par Thayssen en 1926 et en 1929. Il en donne comme critère une flèche hyperglycémique égale ou inférieure à 40 mg après l'absorption de 50 g de glucose. Martin et Sciclounoff (23), dans leur importante étude, admettent une valeur un peu moindre, entre 30 et 40 mg et sur 350 malades relèvent ainsi 22 courbes basses. Pour notre part, nous avons adopté le chiffre de 30 mg. Mais, ainsi que nous allons le voir, le problème des cas limites ne se pose pratiquement pas, car il semble que les courbes puissent se classer en deux catégories bien distinctes (tableau I et II).

a) Courbes plates: 10 sujets, soit 62.5 %. La flèche, nettement inférieure à 30 dans la majorité des cas, peut même être inversée, comme dans le cas 6, où la glycémie fait une chute de 27 après l'absorption du glucose. Dans l'ensemble de ces 10 cas la flèche moyenne est de 6 après 30 minutes, et de 7 après 60 minutes.

b) Courbes non plates: 6 sujets, soit 37.5 %. La flèche est, au contraire, nettement élevée, 47 au minimum; elle atteint même, dans deux cas (13 et 14) les chiffres anormalement importants de 73 et 82, évoquant ainsi un dérèglement antagoniste des cas précédents.

A ces deux groupes aux réponses biologiques si franchement opposées, la clinique n'offre pas de réplique. Même dans la cadre homogène des recto-côlites hémorragiques qui constituent la majorité de nos malades, on n'observe aucune différence, symptomatique ou évolutive, quels que soient l'importance ou le sens de la réponse à la sollicitation glycémique. Signalons, cependant, que les seuls cas où l'administration d'acide folique a coïncidé avec une certaine amélioration de la diarrhée se sont surtout comptés parmi ceux dont la courbe glycémique était préalablement basse.

Tableau I.

*Épreuve d'hyperglycémie provoquée après ingestion de 50 g de glucose (Résultats en mg %).*

		A jeun	30'	60'	90'	120'	150'
<i>Sujets diarrhéiques à courbe plate.</i>							
1. Sau .....	Rectocôlite	115	95	95	80	75	80
2. Kno .....	d°	48	77	65	64	66	—
3. Pez .....	d°	70	82	100	87	87	77
4. Cam .....	Lientérie	116	124	124	100	—	—
5. Nos .....	Rectocôlite	76	100	95	95	76	—
6. Rom .....	d°	85	58	54	75	60	—
7. Boq .....	Côlite ulcér.	87	105	113	96	83	—
8. Lev .....	Diarrhée	99	123	130	122	109	97
9. Bou .....	d°	125	140	152	137	119	100
10. ? .....	d°	117	148	137	129	115	104
Moyenne		93	105	106	97	87	91
<i>Sujets témoins non diarrhéiques.</i>							
19. Auz .....	Constipation	81	148	93	87	84	80
20. Her .....	Lithiase	108	155	141	121	116	111
21. Pin .....	Dyspepsie	83	129	125	125	125	90
22. Col .....	d°	70	118	111	98	90	81
23. Kha .....	Constipation	100	134	145	118	107	100
24. La B. ....	Melaena	116	158	170	117	104	86
25. Cah .....		105	144	114	111	108	106
Moyenne		94	140	128	111	105	93

Tableau II.

*Épreuve d'hyperglycémie provoquée après ingestion de 50 g de glucose (Résultats en mg %).**Sujets diarrhéiques à courbe non plate.*

		A jeun	30'	60'	90'	120'	150'
11. Zyl .....	Rectocôlite	125	147	177	128	112	—
12. Jea .....	d°	92	122	146	84	80	—
13. Pro .....	d°	87	117	170	121	109	94
14. Auc .....	d°	118	202	161	129	108	90
15. Nao .....	Diarrhée	107	165	156	120	109	99
16. Pon .....	Dys. bacillaire?	104	139	151	127	111	94
Moyenne		105	149	160	118	105	94

**B. L'épreuve d'hyperglycémie provoquée par voie intra-veineuse.**

Ce test limite son exploration à la régulation et à l'utilisation tissulaire, excluant ainsi les phénomènes digestifs proprement dits (absorption et transit intestinaux).

*Technique.* La technique employée est celle de Fiessinger, légèrement modifiée par Baixas (2) qui comprend l'injection intra-veineuse de sérum glucosé à 30 %, à concurrence de 1 g de glucose par kg de poids corporel. L'injection du sérum tiédi est poussée en 10 minutes environ. Les prélèvements sanguins, veineux ou capillaires sont, là encore, effectués de 30 en 30 minutes.

Tableau III.

Tableau comparatif d'hyperglycémie provoquée per os, par voie intra-veineuse et de mesure directe de l'absorption intestinale du glucose par la méthode de Miller-Abbott.

	Hyperglycémie provoquée per os	Hyperglycémie provoquée intra-veineuse	Glucose recueilli à la sonde de M. A.
3. Pez .....	Jeun ..... 70	84	g
	30' ..... 82	180	1/2 h. après le début de l'ingestion ..... 4.51
	60' ..... 100	160	Après SO <sub>4</sub> Mg. .... 0.47
	90' ..... 87	135	Après H <sub>2</sub> O ..... 0.92
	120' ..... 87	125	Total 5.90
	150' ..... 77	100	
4. Camp .....	116	87	1/2 h. après le début de l'ingestion ..... 5.68
	124	159	Après SO <sub>4</sub> Mg. .... 2.91
	124	121	Après H <sub>2</sub> O ..... 0.37
	100	105	Total 8.99
		96	
		94	
6. Rem .....	85	142	
	58	52	
	54	70	
	75	75	
	60	57	
		58	
Normes .....	Flèche > 30	Flèche autour de 211	Total autour de 10 g

La flèche notée par Baixas, dans des conditions à peu près identiques, oscille de 120 à 314 avec une moyenne de 211, le retour au taux initial se faisant en 1 h. 15 environ.

Résultats (tableau III). Cette recherche a été limitée aux sujets qui avaient déjà présenté, après ingestion de glucose, des courbes d'hyperglycémie « plates ».

Chez les trois malades ainsi explorés, la flèche s'est révélée anormalement basse dans 2 cas (obs. 3 et 4) et même négative dans un cas (obs. 6).

### C. Étude de l'absorption intestinale du glucose à l'aide de la sonde de Miller-Abbott.

Cette épreuve, préconisée et normalisée par Miller et Abbott (24), Groen et Juda (17), Nicholson et Chornock (27), étudiée d'une manière très élective la « tolérance » de la muqueuse intestinale à l'égard du glucose.

Malheureusement, la complexité de son appareillage, et surtout la fatigue qu'elle impose au malade en raison d'un tubage intestinal de près de 3 heures, ne permettent pas son application courante.

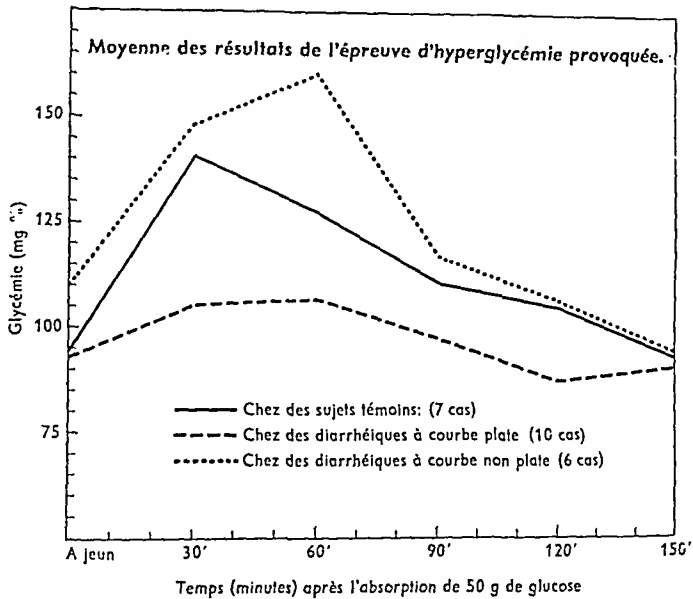
Technique. Le principe de l'épreuve est de faire passer une quantité connue de glucose, dans une longueur déterminée d'intestin grêle, durant un temps donné; le

glucose recueilli à l'issue de ce trajet étant dosé, il est ainsi aisé de déduire la quantité absorbée.

Nous en avons réalisé l'application pratique de la manière suivante:

Une sonde opaque et souple à double lumière (sonde de Miller-Abbott), dont une conduite commande un ballonnet terminal gonflable, et l'autre deux séries d'orifices situées l'une en amont et l'autre (olive terminale) en aval du ballon de baudruche, est introduite dans l'estomac.

A un mètre de l'extrémité gastrique de cette première sonde, on fixe sur elle, à l'aide de fil ciré, l'extrémité olivaire d'une deuxième sonde, également opaque, à une seule lumière, sonde de Camus en général.



Courbe A.

Grâce au ballonnet terminal légèrement distendu et saisi par le péristaltisme gastrique puis intestinal, l'ensemble du système est entraîné à travers le tractus digestif et peut être suivi à la radioscopie.

Lorsque l'extrémité de la deuxième sonde atteint le deuxième duodénum, on gonfle le ballon à distension maximum, soit de 70 à 80 cc d'air, de manière à le bloquer dans le jéjunum.

Ainsi est limitée entre les 2 sondes une longueur d'un mètre de muqueuse intestinale. Le liquide injecté par la sonde supérieure et non absorbé par la muqueuse sera récupéré au niveau des orifices de la sonde à double courant situés en amont du ballonnet, dont la distension évite toute fuite. L'aspiration est faite à l'aide d'un aspirateur à vibrations capable de débiter 500 cc à la minute.

D'autre part, la vérification de la distension permanente du ballon est assurée en branchant un manomètre à eau sur la conduite permettant son gonflage, l'injection d'air maintenant la colonne d'eau à un niveau constant.

Une fois ce dispositif ainsi mis en place, le déroulement de l'épreuve est le suivant:

Injection par la sonde supérieure de 300 cc d'une solution, teintée en rose, de glucose à 10 % (soit 30 g de glucose) en 30 minutes, à raison de 10 cc par minute; puis, au même rythme, d'une solution de sulfate de magnésie à 30 %, enfin de 100 cc d'eau, ces deux dernières instillations ayant pour but de rincer complètement la muqueuse intestinale.

Aspiration continue par la sonde inférieure; recueil du liquide dès qu'apparaît la coloration rose. Ce dernier est divisé en trois fractions correspondant aux trois séries consécutives d'instillation.

Dans des conditions expérimentales très peu différentes et avec un matériel identique, Nicholson et Chornock (27) retrouvent, chez des sujets normaux, 13 g 8 de glucose sur les 30 g administrés par la sonde, soit une absorption de 46 %.

*Resultats* (tableau III). Nous n'avons pu pratiquer cette épreuve que chez 2 malades: l'un (obs. 3) atteint de recto-côlite hémorragique, l'autre (obs. 4) de diarrhée d'allure lienterique datant de l'enfance.

Chez ces deux sujets, la quantité de glucose non absorbée s'est élevée respectivement à 5 g 90 et 8 g 99 correspondant à une absorption comprise entre 70 et 80 %, supérieure à celle qu'ont observée Nicholson et Chornock.

C'est dire que, dans ces cas, le comportement de la muqueuse intestinale à l'égard du glucose s'est révélé absolument normal.

#### D. Dosage de la pyruvicémie. §

Depuis plus d'une décade, les recherches de MM. Polonovski et Warembourg (30) sur l'indice chronique résiduel ont montré l'intérêt de posséder un test usuel, permettant l'étude des perturbations profondes qui modifient, jusqu'à l'échelle cellulaire, le cours normal du métabolisme glucidique dans certains états pathologiques.

Le dosage de l'acide pyruvique sanguin semble pouvoir remplir, en partie tout au moins, ces conditions, ainsi que l'ont montré les travaux de Klein et Elsom (18), Bueding et Wortis (8), Stotz (33); ces auteurs notent, en effet, d'importantes modifications des pyruvates sanguins après administration de glucose ou d'insuline, chez l'homme normal, le diabétique et dans différents états pathologiques.

Rien n'est plus logique d'ailleurs puisque, dans la phase anoxybiotique de la contraction musculaire, l'acide pyruvique est le terme obligatoire et dernier de transformation du glucose en acide lactique.

Cependant, outre que l'acide pyruvique n'est pas le témoin exclusif du métabolisme glucidique, il peut être modifié, dans le cadre même de ce métabolisme, par un certain nombre d'éléments.

Tout d'abord intervient la carence en vitamine B<sub>1</sub>; cette dernière, jouant le rôle de cocarboxylase, est en effet indispensable à la décarboxylation de l'acide pyruvique. Ce fut le mérite des travaux de Peters (28), de Lohmann et Schuster (19) de montrer qu'une des premières manifestations de la carence en thiamine est une accumulation anormale d'acide pyruvique dans le sang, le cœur et l'encéphale.

Notons immédiatement que ce facteur n'est capable de créer qu'une hyperpyruvicémie et que jamais il ne peut modifier le taux en sens inverse.



D'autre part, J. Marche et Mlle C. Marnay (22), dans un travail récent, ont montré que chez les hépatiques une hyperpyruvicémie peut également être notée surtout si la maladie est ictérique et prolongée.

Or, ces deux causes d'erreur — carence et troubles hépatiques — pourraient éventuellement intervenir chez nos malades depuis que de nombreuses observations (Caroli, Busson et Girard (10); Moutier (26); Minet, Warenbourg et Linguette (25) et à l'étranger celles de Carere-Comes (9)) nous ont appris que l'association de diarrhée et de signes de béri-béri fruste, de diarrhée et de dégénérescence hépatique ou encore, sous un angle plus clinique, de diarrhée et d'anasarque, sont loin d'être faits exceptionnels.

C'est pour échapper en partie aux critiques que ces faits pourraient légitimer que nous avons effectué, parallèlement à celui de la pyruvicémie, le dosage de la sérine et de la globuline, du cholestérol libre et estérifié, qui nous ont renseignés sur l'état de la cellule hépatique.

En conclusion de cette introduction critique, nous pensons que l'on peut considérer la pyruvicémie comme un témoin du métabolisme glucidique cellulaire, pour autant que les autres facteurs susceptibles d'intervenir aient été éliminés, ces facteurs n'étant d'ailleurs capables de créer qu'une hyperpyruvicémie.

*Technique.* L'acide pyruvique a été dosé dans le sang total suivant la technique de G. D. Lu (20), modifiée par Mlle A. Vinet et Y. Raoul (37), sous la direction de Mlle C. Marnay.

Le prélèvement sanguin a été effectué sur le sujet à jeun et au repos depuis une demi-heure, le sang recueilli sur fluorase et mono-iodacétate de soude, les tubes portés immédiatement dans la glace.

Dans ces conditions, le taux sanguin normal varie entre 0.70 mg et 7.10 mg, en moyenne 0.80—0.85 mg pour 100 cc de sang total. Selon Marche et Mlle C. Marnay (22), les taux supérieurs à 1 mg 20 peuvent être considérés comme anormaux, sinon pathologiques.

*Résultats* (tableau IV). Les chiffres obtenus s'étalent entre 0 mg 52 et 1 mg 68. Notons dès maintenant, comme les taux de cholestérolémie et de protidémie étaient par ailleurs normaux, que la pyruvicémie semble bien dépendre, chez tous nos sujets à l'étude, du seul métabolisme glucidique.

Ces résultats prennent toute leur signification lorsqu'on les compare aux courbes glycémiques.

En effet, aux courbes glycémiques »plates« correspondent six fois sur sept des taux faibles ou anormalement bas de la pyruvicémie (entre 0.52 mg et 0.84 mg) la moyenne des sept cas s'établissant à 0.78 mg. Au contraire, les courbes glycémiques normales ou élevées s'associent habituellement à des taux pyruviques également élevés, compris dans quatre cas sur six entre 1.26 mg et 1.68 mg la moyenne se chiffrant à 1.31 mg.

On discutera ultérieurement de l'interprétation qu'il est possible de donner de ce parallélisme.

Tableau IV.

Tableau comparatif de pyruvicémie, hyperglycémie provoquée, protides et cholestérol sanguins.

		Hyperglycémie provoquée	Pyruvicémie (mg %)	Protides (g p. l)		Cholestérol (g p. l)	
				S	G	Total	Esters
1. Sau .....	Rectocôlite	C. plate	0.73	47	37	1.55	1
2. Kno .....	d°	C. plate	0.80	60	23	2.10	1.30
3. Pez .....	d°	C. plate	0.84	—	—	2.10	1.20
4. Com .....	Lientérite	C. plate	1.06	45	25.5	1.80	0.90
5. Nos .....	Rectocôlite	C. plate	0.78	—	—	2.50	1.10
6. Rem .....	d°	C. plate	0.52	—	—	—	—
7. Boc .....	Côlite ulcé- reuse	C. plate	0.73	43.2	42.8	1.55	0.70
Moyenne des malades à courbe plate .....			0.78				
11. Zyl .....	Rectocôlite	C. non plate	1.50	45	47	2.70	1.30
12. Jea .....	d°	C. non plate	0.94	54	26	1.30	1.10
13. Pro .....	d°	C. non plate	1.26	—	—	—	—
14. Auc .....	d°	C. non plate	1.05	—	—	—	—
17. Bec .....	Côlite ulc.	C. non plate	1.47	55	25	1.85	1
18. Tim .....	Amibiase	C. non plate	1.68	42.5	40	1.90	1
Moyenne des malades à courbe non plate .....			1.31				

## II. Interprétation des résultats.

C'est au cours de la sprue, on l'a vu plus haut, que furent notées pour la première fois par Thayssen les «courbes glycémiques basses» et c'est également au cours de cette maladie que l'étude pathogénique de cette anomalie fut le plus approfondie. Il est donc légitime de prendre, comme terme de référence de nos résultats, les données biologiques recueillies dans les stéatorrhées idiopathiques.

Quelle interprétation donne-t-on actuellement de ces troubles nutritionnels?

Thayssen, en 1934, se refusait à y voir un trouble de l'absorption intestinale pour les cinq raisons suivantes:

1. Facilité de la résorption du glucose,
2. Existence de courbes glycémiques basses même durant les périodes de rémission, sans stéatorrhée,
3. Élévation normale du quotient respiratoire après absorption de 70 g de glucose,
4. Existence de courbes également anormalement basses par injection de glucose intra-veineux,
5. Flèche glycémique très élevée après injection d'adrénaline signant l'intégrité des réserves hépatiques.

Depuis lors, de nombreux travaux ont infirmé les conclusions de Thayssen et, pour ne s'en tenir qu'aux travaux récents sur la sprue, ceux de Spies (32), de Darby

et ses collaborateurs (14), (15) aux États-Unis, de Mme Bertrand-Fontaine (4) en France, on peut admettre que, parmi les troubles nutritionnels accompagnant ce type de stéatorrhée, il en est 3 principaux:

Diminution de l'absorption intestinale du glucose,

Diminution de l'absorption intestinale des graisses et troubles du métabolisme de la vitamine A,

Corrections des deux altérations précédentes par l'administration d'acide folique.

Les constatations faites par nous au cours des diarrhées » banales » offrent-elles quoi que ce soit qui rappelle ces trois faits et permette ainsi d'évoquer, selon l'hypothèse de Verzár, un trouble de la phosphorylation dans la paroi intestinale?

#### A. Existe-t-il un trouble de l'absorption du glucose?

Nos résultats semblent prouver formellement qu'il n'en est rien. L'identité des courbes d'hyperglycémie obtenues par voie orale et par voie veineuse laissent déjà supposer que la muqueuse intestinale est hors de cause et la mesure directe de l'absorption du glucose par la méthode de Miller-Abott confirme cette intégrité (Tableau III).

Des constatations du même ordre ont déjà été publiées. Baixas (2), Bercowitz et Page (3) ont observé des courbes glycémiques identiques aux nôtres dans les rectites hémorragiques. En outre, ces derniers auteurs, par la mesure du métabolisme basal et du quotient respiratoire après absorption de glucose, ont montré qu'était normale chez ces malades l'utilisation tissulaire des hydrates de carbone et, a fortiori, leur résorption intestinale.

#### B. Existe-t-il un trouble de l'absorption des graisses et du métabolisme de la vitamine A?

L'analyse systématique des selles n'a jamais montré, chez aucun de nos malades, de stéatorrhée, mais ce trouble a, pour Chesney et McCord (13), moins d'importance dans la sprue que les anomalies du métabolisme de la vitamine A.

##### 1. — Étude de la vitaminémie à jeun.

En accord avec la plupart des auteurs, et J. Marche (21) en particulier, nous classons nos résultats selon les données suivantes, chiffrées en U. I pour 100 cc de plasma:

Plus de 100 = normal

70 à 100 = subnormal

40 à 70 = subcarence

Moins de 40 = carence ou trouble grave du métabolisme de la vitamine A.

Les dosages ont été effectués par la méthode Raoul et Janot (31) légèrement modifiée.

Le tableau V montre que 50 % de nos malades ont un taux carentiel ou sub-

Tableau V.  
Métabolisme de la vitamine A.  
I. Vitaminémie à jeun.

Catégories	Nombre de dosages	Vitaminémie (en U. I p. 100 ml plasma)			
		moins de 40	40 à 70	70 à 100	plus de 100
Diarrhées .....	21	3	8	7	3
Témoins .....	21	0	3	7	11

II. Épreuve d'hypervitaminémie provoquée (ingestion de 200,000 U. I de Vitamine A)

		Vitaminémie (en U. I p. 100 ml de plasma)			
		A jeun	3è. II.	6è. II.	24è. II
Obs. 3. Pez .....	74.5	824	926	114	
Obs. 4. Com .....	60	540	762	98	
Témoins (moyenne de 10 épreuves)	109.4	584	801.1	150.6	

carentiel, alors que 14 % seulement des témoins, non diarrhéiques, sont dans le même cas.

Ces résultats sont en désaccord avec ceux de Cayer, Ruffin et Perlzweig (12) qui, dans huit cas de dysenteries, amibiennes il est vrai, trouvent une vitaminémie A normale, alors qu'ils notent une moyenne de 48 U. I dans douze cas de sprue.

2. — Épreuve d'hypervitaminémie A provoquée.

Cette épreuve, dont l'importance au cours de la sprue a, pour la première fois, été soulignée par Chesney et McCord explore d'une manière très générale le métabolisme de la vitamine A.

Selon des travaux français récents (6), elle peut être réalisée de la manière suivante:

Après dosage à jeun, 200,000 U. I de vitamine A sont absorbées par le sujet au cours d'un repas comprenant un morceau de pain et un bol de café. Les prises de sang sont ensuite faites 3, 6 et 24 heures après l'ingestion, mais compte surtout le résultat noté à la 6ème heure, période d'élévation maxima de la flèche d'hypervitaminémie.

Nos résultats, schématisés dans le tableau V, montrent que la flèche obtenue dans les deux cas de diarrhée explorés est normale, ce qui implique une absorption intestinale correcte de la vitamine A.

Il est à noter que ces deux mêmes sujets présentaient également une absorption intestinale normale du glucose, prouvée par les études des hyperglycémies orales et intra-veineuses comparées, ainsi que par la mesure directe de l'absorption intestinale de cet hexose.

Nos données à l'égard de l'épreuve d'hypervitaminémie A provoquée sont con-

firmées par les résultats d'Alersberg et Sobotka (1) qui, dans leur étude comparée de la sprue et des jéuno-iléites, montrent que, si les troubles du métabolisme de la vitamine A dans la sprue aboutissent à une flèche d'hypervitaminémie très basse ou nulle, cette flèche est normale dans les jéuno-iléites.

Ces faits viennent donc accentuer encore la différence des troubles métaboliques de la sprue, attribuables à un défaut de phosphorylation au niveau de la muqueuse intestinale, et ceux des diarrhées banales, au sujet desquels nous émettrons ultérieurement quelques hypothèses.

### C. L'acide folique corrige-t-il les troubles métaboliques des diarrhées banales?

Le fait que l'administration d'acide folique (ptéroylglutamique) améliore, sinon guérit, au cours de la sprue, et le syndrome clinique et les troubles nutritionnels — courbes glycémiques plates en particulier —, incite à rechercher si cette thérapeutique vitaminique ne pourrait exercer une action identique au cours des diarrhées banales.

Les premiers essais dans ce sens ont été tentés par Carruthers (11) qui relève une action favorable sur le nombre des selles et l'aspect rectoscopique de 6 cas de diarrhées hétérogènes; pour cet auteur, l'acide folique agirait sur le retentissement nutritionnel de la diarrhée, ce qui permettrait d'invoquer une parenté avec les troubles de la sprue.

Par contre, Davidson (16) constate, plus récemment, l'inefficacité de doses même élevées d'acide folique au cours de la recto-côlite hémorragique.

Nos essais portent sur 7 cas de recto-côlites hémorragiques qui ont reçu de 5 à 20 mg par jour d'acide ptéroylglutamique, durant une période variant d'une semaine à un mois.

Une diminution assez nette du nombre des selles fut notée dans trois cas, sans que pourtant disparaissent jamais les lésions rectoscopiques et en particulier la fragilité de la muqueuse, qui continue de saigner à la moindre pression de l'écouvillon.

Dans deux autres cas, la dose quotidienne de 15 mg sembla déclencher une aggravation du syndrome fonctionnel qui s'améliora, au contraire, avec 5 mg.

Dans deux observations, enfin, la thérapeutique fut indifférente.

L'étude des modifications biologiques apportées par l'administration d'acide folique nous paraît, par contre, beaucoup plus intéressante (Tableau VI) (Courbe B).

Chez quatre malades, qui présentaient initialement une courbe glycémique basse, on voit apparaître en fin de traitement une hypoglycémie considérable à la 2ème heure, atteignant dans un cas le chiffre extraordinairement faible de 40 mg % sans que jamais cependant ait été noté aucun trouble fonctionnel, tandis que la flèche d'hyperglycémie reste sensiblement aussi écrasée.

Ces résultats sont donc bien différents de ceux que l'on observe au cours de la sprue, où la flèche glycémique retrouve, après administration d'acide folique, son profil ascensionnel normal. Cependant, ils nous paraissent intéressants de rapprocher de nos données un cas de Darby (14), concernant une sprue traitée par l'acide folique

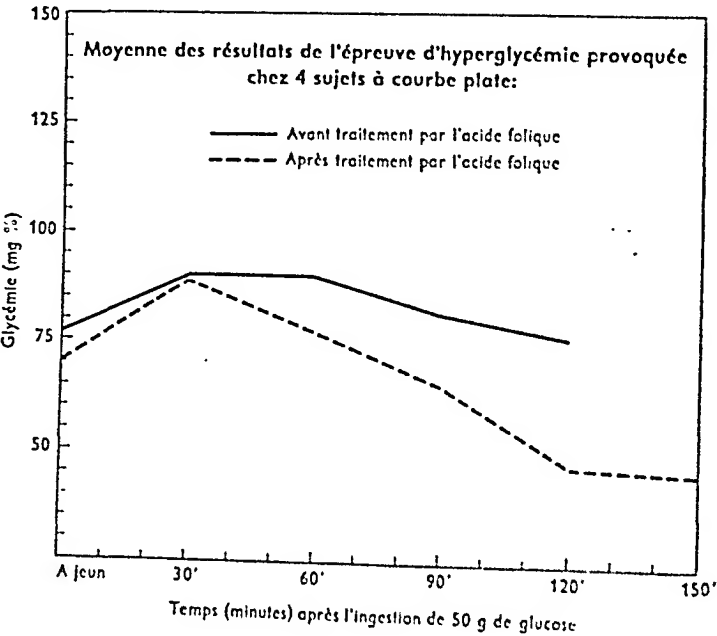
Tableau VI.

Action de l'acide folique sur les courbes d'hyperglycémie provoquée (mg %).

I. Sujets à courbe initialement plate.

	A jeun	30'	60'	90'	120'	150'
Avant Ac. F.: Moyenne des cas 1, 2, 3, 5	77	88	88	81	76	
Après Ac. F. 1 .....	66	91	76	40	40	40
2 .....	76	115	113	105	56	50
3 .....	60	80	68	58	50	42
5 .....	74	67	52	58	55	54
Moyenne .....	69	88	77	65	48	46
II. Sujets à courbe initialement non plate						
Avant Ac. F.: Moyenne des cas 11, 13, 14	110	155	169	126	109	92
Après Ac. F. 11 .....	112	120	148	140	100	
13 .....	90	141	178	130	109	91
14 .....	94	145	159	112	96	88
Moyenne .....	99	135	161	127	101	90

pendant 35 jours dans laquelle, après traitement, le taux de la glycémie atteignait, après surcharge glucosée, 62 mg à la 3ème heure, alors que le chiffre de départ, à jeun, était de 90 mg.



Courbe B.

Dans trois cas de recto-côlites hémorragiques à courbe glycémique normale ou élevée avant le traitement, l'acide folique n'a au contraire modifié qu'insensiblement la silhouette de la courbe, abaissant simplement, et très légèrement d'ailleurs, la hauteur de la flèche d'hyperglycémie.



Les courbes d'hyperglycémie plate ne traduiraient donc qu'un des aspects des courbes d'hyperinsulinisme.

Mais les points d'application de l'insuline, dans le métabolisme des glucides, sont multiples et, en particulier, un de ses rôles serait pour Mayer, Dakin, E. Lambling, de permettre la dégradation de l'acide pyruvique au cours de la glycogénolyse. L'hyperinsulinisme devrait donc s'accompagner d'une destruction exagérément rapide de l'acide pyruvique; or, n'est-ce pas dans notre groupe de malades à courbes glycémiques plates que nous observons un abaissement à peu près constant et parfois notable du taux de la pyruvicémie?

Ainsi donc la survenue de ces deux perturbations relevant d'étapes très différentes du métabolisme glucidique pourrait trouver son explication dans un trouble endocrinien basal.<sup>1</sup>

Nous trouvons deux autres arguments pour étayer cette hypothèse; d'une part, l'existence, connue depuis longtemps et soulignée par Bohn et Juza-Uhlig (5) en 1938, de signes cliniques d'hypoglycémie survenant 1 à 2 heures après les repas, chez les diarrhéiques chroniques, confirmée d'ailleurs par les dosages sanguins montrant une courbe d'hyperglycémie provoquée avec un abaissement secondaire, vers la 2ème heure, nettement au-dessous du taux initial.

L'interprétation de ces hypoglycémies réactionnelles est généralement liée «au fait que la quantité d'insuline élaborée par l'organisme pour réduire l'hyperglycémie est supérieure aux besoins réels de l'organisme» (Boulin) (7).

D'autre part, l'étude des courbes d'hyperglycémie après administration d'acide folique nous a permis de noter l'apparition d'hypoglycémies réactionnelles considérables, de ce même type d'hyperinsulinisme, et ceci uniquement chez les sujets à courbes glycémiques basses. Quel que soit le mode d'action de l'acide folique — problème qui déborde le cadre de ce travail — nous pensons, à cause de l'exclusivité même du terrain sur lequel il déclenche des modifications biologiques, qu'il ne saurait créer à lui seul l'hyperinsulinisme; en effet, l'étude des courbes d'hyperglycémie chez des sujets diarrhéiques à courbes glycémiques non plates, d'une part, chez deux Biermériers, d'autre part, ne nous a jamais montré de modifications de la silhouette de cette courbe après traitement par l'acide folique. Ce dernier ne saurait donc que favoriser et accentuer un état préexistant dont témoigneraient les courbes basses.

Ainsi vient s'ajouter un nouveau chaînon pour plaider en faveur de l'hyperinsulinisme dans l'explication des courbes glycémiques basses.

Mais, si notre hypothèse est exacte, si l'hyperinsulinisme crée les courbes glycémiques basses, l'hypopyruvicémie, les réactions hypoglycémiques après administration d'acide folique, en cas de courbes non basses, on doit pouvoir relever une inversion des modifications biologiques associées.

C'est exactement ce que nous notons. Chez ces sujets, dont certains ont non seulement une courbe non plate mais parfois anormalement élevée, l'hyperpyruvicémie est la règle puisque la moyenne de nos six cas est de 1 mg 31, l'acide

<sup>1</sup> En effet, par hyper- ou hypo-insulinisme, nous entendons une modification dans l'un ou l'autre sens de l'ensemble de l'équilibre hormonal de la régulation du métabolisme du glucose, sans préjuger du taux réel de la sécrétion d'insuline.



folique enfin ne crée aucune perturbation. Une dernière confirmation serait apportée si l'étude systématique de tels malades montrait que l'élévation du quotient respiratoire après absorption de glucose est inférieure à la normale. Mais ce travail n'a pas, à notre connaissance, encore été fait.

Par ailleurs, de nombreux auteurs dont Bohn et Juza-Uhlig (5), Bercowitz (3) ont noté chez les diarrhéiques l'existence de courbes du type paradiabétique qui, pour ce dernier auteur, atteint 31 % des cas (le taux de courbes basses noté dans cette statistique est de 39.6 %).

L'ensemble de ces faits plaide pour l'existence d'un syndrome d'hypo-insulinisme, symétriquement opposé du syndrome d'hyperinsulinisme précité.

*En conclusion*, donc, il nous semble possible de dire que les troubles du métabolisme du glucose sont très fréquents au cours des diarrhées dites « banales ». Ils peuvent être mis en évidence par l'étude de l'épreuve d'hyperglycémie provoquée, par le dosage de la pyruvicémie et, plus accessoirement, par l'administration d'acide folique.

Ces troubles relèvent très probablement d'une perturbation endocrinienne où l'insuline joue le premier rôle.

Il est possible de relever, selon les cas, un syndrome d'hyperinsulinisme et un syndrome d'hypo-insulinisme. Ces syndromes, déclenchés par la diarrhée, ne sauraient guérir qu'avec elle; mais on doit tenter d'atténuer le retentissement de cette diarrhée sur la nutrition générale, d'autant que ce retentissement peut à son tour favoriser la diarrhée.

Aussi semble-t-il logique, en tenant compte des données biologiques, de pratiquer par exemple, selon les cas, outre le traitement étiologique de base, des administrations d'insuline à petites doses répétées ou, au contraire, un régime sucré avec administration de sérum glucosé parentéral.

### Summary.

I. The Metabolism of Carbohydrates was studied in cases of chronic diarrhoeas of the usual type. Titration of hyperglycemia induced by oral and intravenous introduction of glucose, titration of pyruvic acid in blood and direct measure of the absorption of glucose through the intestine were done of all the patients.

II. No trouble in the absorption of glucose or lipids through the intestine could be demonstrated, even in cases with low hyperglycemia response (62.5 %).

III. A survey of the metabolism of vitamin A and of the effects of folic acid confirms that the metabolic disturbances recorded in chronic diarrhoeas and idiopathic steatorrhea are not identical.

IV. Chronic diarrhoeas may be divided in two groups:

- 1) One with small hyperglycemia response to glucose; low level of pyruvic acid in blood and hypoglycemia following the intake of folic acid.
- 2) The other with normal or high hyperglycemia response to glucose, high level of pyruvic acid in blood, no hypoglycemia response to folic acid.

V. It is suggested that some endocrine disturbance underlays the preceeding conditions bearing mainly on the secretion of insulin.

### Bibliographie.

1. Adlersberg, D., Sobotka, H.: L'absorption des graisses et de la vitamine A dans la sprue et les jéjuno-iléites. *Gastroenterol.* 1, 357, 1943. — 2. Baixas, H.: L'épreuve d'hyperglycémie provoquée par injection intraveineuse. Thèse Montpellier 1939—40, n° 59. — 3. Bercowitz, Z., Page, R. C.: Études métaboliques et vitaminiques au cours des colites chroniques ulcéraives. *Ann. of Intern. Med.* 20, 239, 1944. — 4. Bertrand-Fontaine, Mme, Cachérat, R., Fauvert, R. et Mlle Noufflard: Étude d'un cas de sprue autochtone. *Soc. Med. Hôp. Paris. Séance du 23. V. 1947.* — 5. Bohn, H., Juza-Uhlig, G.: Réactions hypoglycémiques au cours des entérites chroniques. *Zentralbl. f. Inn. Med.* 59, 465, 1938. — 6. Bonfils, S., Marnay, Ch.: Résultats de l'épreuve d'hypervitaminémie A provoquée chez des sujets normaux et pathologiques. *Soc. de Biol. Séance du 24. I. 48.* — 7. Boulin, R.: Précis de pathologie médicale, T. VI. Masson. — 8. Bueding, E., Wortis, H., Fein, H. D., Esturonne, R.: Métabolisme de l'acide pyruvique dans le diabète sucré. *Amer. J. Med. Sci.* 204, 838, 1942. — 9. Carere-Comes, O.: Affections gastriques et intestinales et avitaminose B<sub>1</sub>. *Klin. Wochenschr.* 22, 339, 1943. — 10. Caroli, J., Busson, A., Girard, P.: Contribution anatomo-clinique à l'étude de l'atteinte hépatique au cours des colites ulcéreuses graves. *Arch. Mal. Tube digest. et Nutrit.* 21, 762, 1937. — 11. Caruthers, L. B.: Diarrhées chroniques traitées par l'acide folique. *Lancet*, 250, 819, 1944. — 12. Cayer, D., Ruffin, J. M., Perlzweig, W. A.: Le niveau vitaminique dans la sprue. *Am. J. Med. Sci.* 210, 200, 1945. — 13. Chesney, J., McCord, A.: Vitamine A du sérum après absorption d'huile de poisson chez les enfants normaux et au cours des stéatorrhées chroniques. *Proc. Soc. Exper. Biol. Med.* 31, 887, 1934. — 14. Darby, W. J., Jones, L., Johnson, H. C.: Effets du *Lactobacillus casei* factor synthétique sur la sprue. *J. A. M. A.* 130, 780, 1946. — 15. Darby, W. J., Kaser, M. M., Jones, L.: Influence de l'acide ptéroyl-glutamique sur l'absorption de la vitamine A et du carotène au cours de la sprue. *J. of Nutrit.* 33, 243, 1947. — 16. Davidson, Guiverod: L'acide folique comme agent thérapeutique des diarrhées. *Brit. M. J.* 1, 587, 1947. — 17. Groen, H., Juda: L'absorption des hexoses par la portion supérieure de l'intestin de l'homme. *J. Clin. Invest.* 16, 245, 1937. — 18. Klein, D., Elsom, K. S.: Étude de la vitamine B chez l'homme; Taux de pyruvicémie et lactate-pyruvicémie après ingestion de glucose dans la carence expérimentale. *Amer. J. Med. Sci.* 207, 247, 1944. — 19. Lohmann, K., Schuster, P.: *Biochem. Zeit.* 294, 188, 1937. — 20. Lu, G. D.: *Biochem. J.* 33, 249, 1939. — 21. Marche, J.: Recherches sur certains métabolismes vitaminiques chez les hépatiques. *Assoc. d'Études physio-pathologiques du foie et nutrition.* 17-XI-45. — 22. Marche, J., Marnay, Ch.: L'acide pyruvique sanguin chez les hépatiques et plus spécialement chez les ictériques. *Bull. de l'Assoc. d'études physio-pathologiques du foie*, 2, 2, 1946. — 23. Martin, Sciclounoff: Intérêt clinique des courbes basses d'hyperglycémie provoquée. *Pr. Médic.* n° 27, 505, 1939. — 24. Miller, T. G., Abbott, W. O.: L'intubation intestinale, une technique pratique. *Am. J. Med. Sci.* 187, 595, 1934. — 25. Minet, J., Warembourg, H., Linguette, M.: Étude biologique et anatomique d'un cas d'anasarque par colite ulcéreuse. *Paris Méd.* n° 16, 168, 1944. — 26. Moutier, F.: Un cas de rectocolite hémorragique avec anasarque, ascite, intolérance aux sulfamides. *Arch. Mal. Tube Digest. Nutrit.* 31, 63, 1942. — 27. Nicholson, J. J. L., Chornock, F. W.: Les études de l'intestin grêle par intubation: une technique sûre pour l'étude des absorptions. *J. Clin. Invest.* 21, 505, 1942. — 28. Peters, A. A.: Altérations biochimiques de la carence en vitamine B. *Lancet*, 1, 1161, 1936. — 29. Polonovski, M.: *Biochimie Médicale.* Masson édit. 1941. — 30. Polonovski, M., Warembourg, M.: L'indice chronique résiduel, nouveau test d'insuffisance glycolytique. *Pr. Méd.* n° 39, 793, 1933. — 31. Raoul, Y., Janot, M. M.: *Bull. Soc. Chim. Biol.* 23, 78, 1941. — 32. Spies, D. J.,

Lopez: Acide folique et sprue. J. A. M. A. 131, 1201, 1946. — 33. Stotz, E.: Le métabolisme pyruvique. Advance in Enzymology V, 129, 1946. Interiscience, édit. — 34. Thayssen, Th., Hens, E.: La stéatorrhée idiopathique de la sprue tropicale et non tropicale et l'infantilisme intestinal. Arch. Mal. Tube digest. Nutr. 24, 123, 1934. — 35. Turpin, R., Guillaumin, Ch. O., Lafon, J. L.: Contribution à l'étude de sprue nostras. Pr. Médic. n° 48, 594, 1941. — 36. Verzár, F., McDougall: L'absorption intestinale. Langmanns et Green Londres, 1936. — 37. Vinet, A., Raoul, Y.: Bull. Soc. Chim. Biol. 24, 357, 1942.

---

Acta Medica Scandinavica. Vol. CXXXVI, fasc. II, 1949.

From The Medical Clinic, University of Lund, Sweden.

## The Femoral Pulse Curve in Coarctation of the Aorta.

By

STINA BJÖRK and KNUT LIEDHOLM.

(Submitted for publication February 22, 1949.)

---

Coarctation of the aorta or stenosis of the aortic isthmus is a pathological condition that has become of more current interest since this congenital malformation has proved more common than previously supposed and since Crafoord showed that surgical treatment can cope with the disease, it has also become more desirable that the condition be diagnosed exactly and the symptomatologic details portrayed as accurately as possible.

To the clinical picture — arterial hypertension in the arms in association with normal or subnormal pressure in the legs, a grooving of the ribs in the radiogram due to the enlarged and tortuous intercostal arteries, a small or absent aortic knob, pulsations in the interscapular space, etc., another pathognomic may be added, viz., *the characteristic change in the appearance of the femoral pulse curve.*

The shape of the femoral pulse curve is normally dependent upon the pulse wave initiated by the stroke volume and propagated via the aorta. This curve, like all other pulse curves, is characterized by a relatively abrupt rise and a more gradual fall intervened by a secondary peak, or at least an arrest, due to the reflection of the pulse wave from the periphery. In aortic coarctation, however, the hemodynamic conditions are quite different, the pulse wave being arrested (at least substantially) at the constriction, with the result that the »pulse wave» in the aorta below the narrowing will be formed not by the stroke volume as an entity but by fractions thereof, which will flow via collateral vessels (the internal mammary, the intercostal, scapular, and deep epigastric arteries) into the lower part of the aorta at different moments and at different levels.

This permits us a priori to expect an anomalous shape of the femoral pulse curve. The following three cases will serve to confirm that this really is the case. As a matter of fact, it was the odd shape of the femoral pulse curve in at least one of the cases that first suggested the diagnosis coarctation of the aorta.

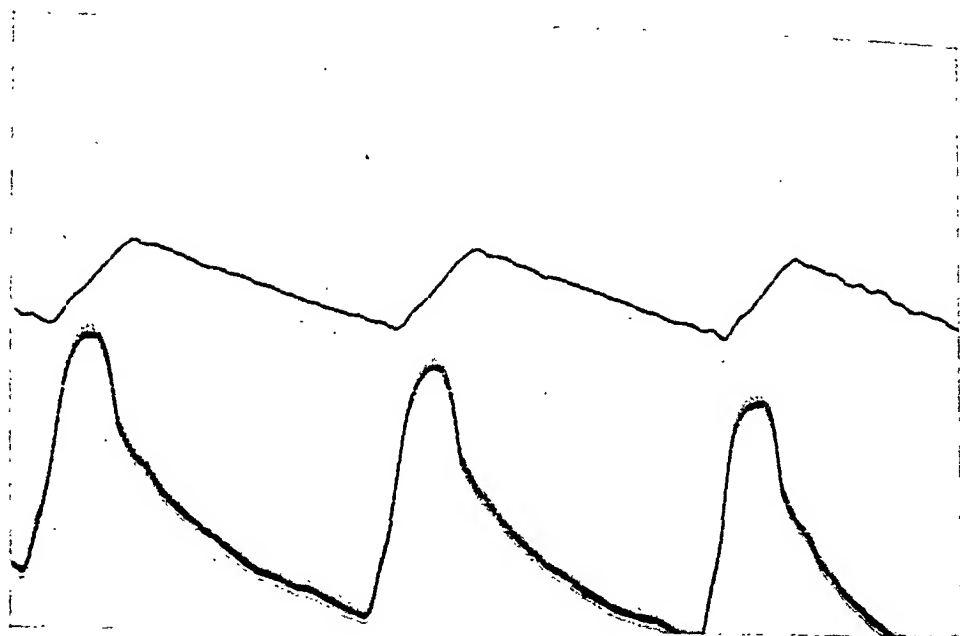


Fig. 1. Aortic Coarctation. Med. journ. 1576/42.

Med. journ. 1576/42, ♀, 29 yrs. Pat. had always been short-winded, physical exertion causing palpitation and heart stitch. Her symptoms had become more troublesome the last three months, during which she had suffered continuously from headache and felt giddy as soon as she bent down or walked quickly. Recently she had also had a slight edema of the ankles in the evening.

*General condition:* unaffected. No cyanosis or dyspnea when resting. No edema.

*Heart:* No pulsation or thrill in the precordium. Sharp first sound. No murmur. Accentuation of the aortic second sound.

*Blood pressure:* right = left arm 180/95 mm Hg.  
right = left leg 125/85 mm Hg.

*Electrocardiogram:* Left axis deviation of an order suggestive of left ventricular hypertrophy. Wide QRS-complex indicating a disorder of the intraventricular conduction.

*X-ray findings:* Enlargement of the left of the heart shadow. No enlargement of the arterial auricle. Abnormally prominent aortic arch, apparently normal descending aorta. Longitudinal shallow grooves along the lower edge of most ribs.

Med. journ. 2257/42, ♀, 14 yrs. During the last four years physical exertion tired the patient unduly and gave her a feeling of weakness in the legs. The last two years she had sometimes suffered from a thumping headache and from giddiness, palpitation and pains in the precordium.

*General condition:* unaffected. No cyanosis or dyspnea when resting. No edema.

*Heart:* Slight precordial pulsations. Apical impulse in the fifth intercostal space in the medioclavicular line, too broad and moderately hard. Sharp first sound at the apex; at the base of the heart, a diastolic murmur of greatest intensity at the second right intercostal space.

*Blood pressure:* right arm 155/90 mm Hg.  
left arm 160/95 mm Hg.  
right leg 135/immeasureable mm Hg.  
left leg 140/immeasureable mm Hg.

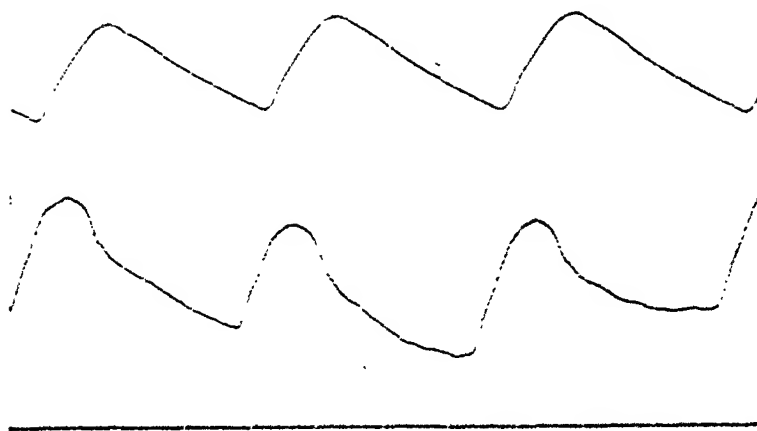


Fig. 2. Aortic Coarctation. Med. journ. 2257/42.

*X-ray findings:* The teleradiogram revealed that the arterial ventricle was slightly enlarged. The aortic knob was strikingly small. In some places the proximal part of the upper ribs of the right side exhibited round grooves.

Med. journ. 1218/44, ♂, 18 yrs. Patient had been short-winded and ever since he could remember he had become tired quicker than his fellow-pupils. When he was 9 years old a congenital disease of the heart was diagnosed. Physical exertion caused palpitation,

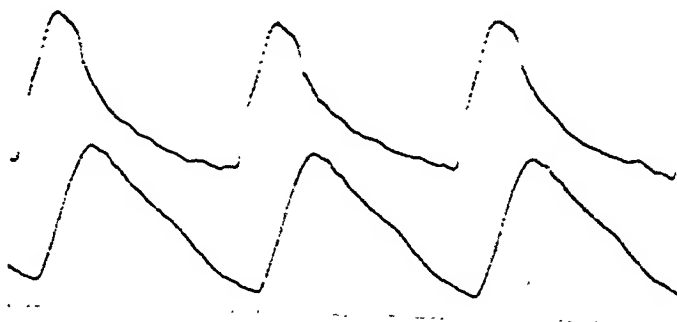
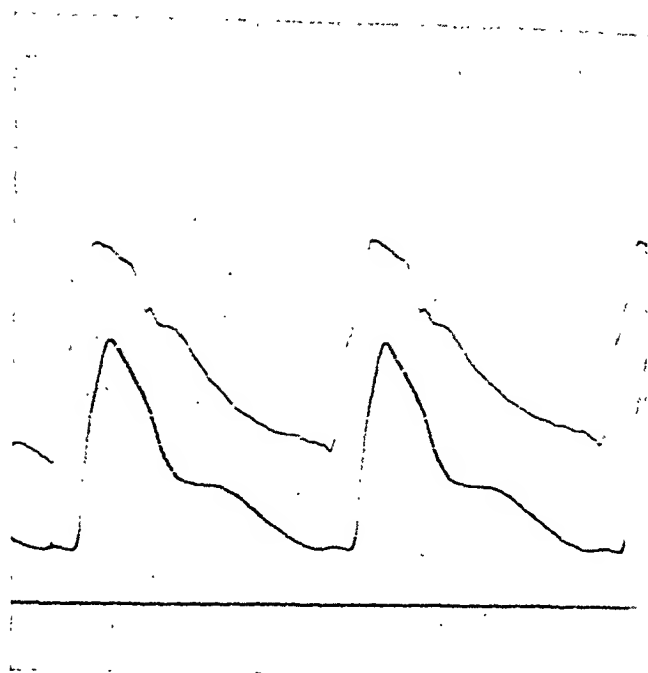
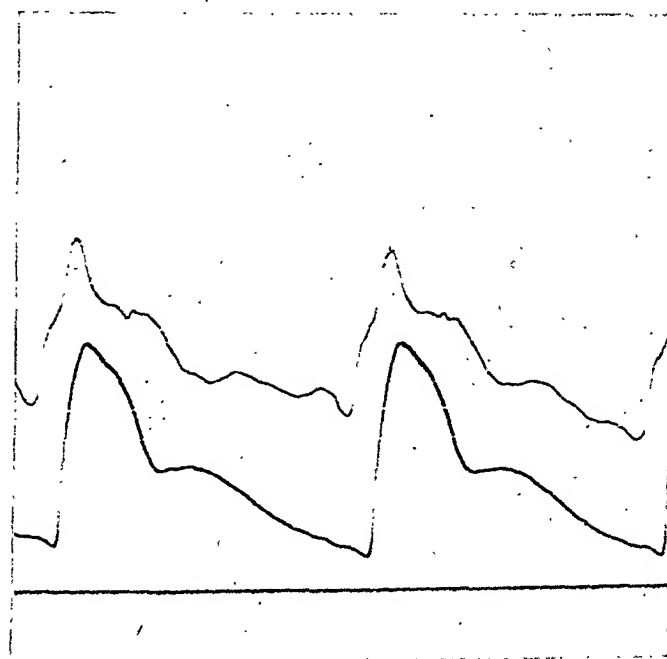


Fig. 3. Aortic Coarctation. Med. journ. 1218/44.



Med. journ. 2250/44, ♂, 31 yrs.



Med. journ. 2258/44, ♂, 24 yrs.

Fig. 4. Individuals with normal circulation.

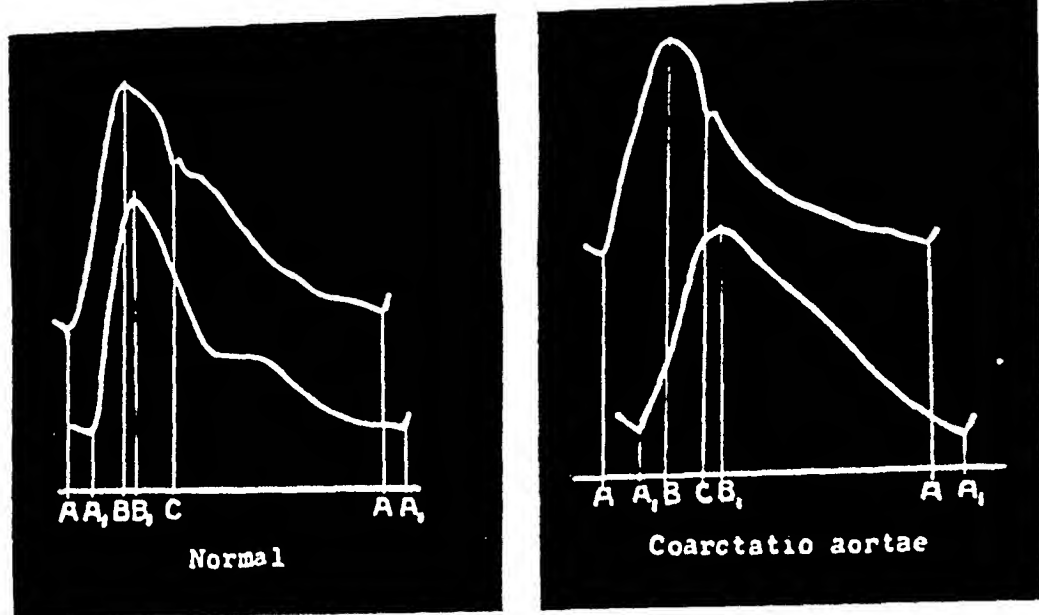


Fig. 5.

- A Foot of the carotid pulse curve.  
 A<sub>1</sub> Foot of the femoral pulse curve.  
 B Peak of the carotid pulse curve.  
 B<sub>1</sub> Peak of the femoral pulse curve.  
 C Termination of the mechanical systole in the carotid pulse curve.

Observe how B<sub>1</sub> precedes C in normals and how this order is reversed in coarctatic patients.

heart stitch, and slight breathlessness. Sometimes he woke up at night and felt he was short of breath. He was inclined to have cold feet.

*General condition:* unaffected. No cyanosis, no dyspnea. No edema.

*Heart:* Pulsations and weak systolic thrill in the precordium. The apical beat at the fourth intercostal space in the mam. line, somewhat broad and strong. Systolic murmur over entire heart with max. intensity at the second right intercostal space. The second aortic sound was accentuated.

*Blood pressure:* right arm 205/140 mm Hg.

left arm 205/120 mm Hg.

Blood pressure in legs immeasurable.

*Electrocardiogram:* No pathological evidence.

*X-ray findings:* Slight enlargement of the heart, probably mainly of arterial ventricle. The aortic knob was less conspicuous than usual. Most ribs were distinctly grooved, indicating hypertrophy of the intercostal arteries.

### Analysis of the Femoral Pulse Curve.

If we study the femoral pulse curves, traced by a Frank's transmission sphygmograph, of patients with aortic coarctation and compare them with the carotid tracings of the same patients (Figs. 1—3) and also with the corresponding curves of two individuals with normal circulation and of about the same ages (Fig. 4), a marked but uniform difference will be apparent.

In the femoral pulse curves of patients with aortic coarctation it should be observed



Table I.

AA ( $A_1A_1$ ) Duration in csec. of the carotid (femoral) pulse wave.  
 AA<sub>1</sub> Delay in csec. of the pulse wave on its way from the aorta to the femoral. From this delay the velocity of the pulse wave (a) of normals can be calculated.  
 AB ( $A_1B_1$ ) Time in csec. necessary for the carotid (femoral) pulse wave to reach its peak.  
 B<sub>1</sub>C Interval in csec. between the peak of the femoral pulse curve and the end of the mechanical systole (as recorded by the carotid pulse curve).  
 a Velocity of pulse wave cm/sec.

	Med. Journ.	Age yrs.	Blood pressure	AA	AC	AB	$A_1B_1$	B <sub>1</sub> C	AA	a
Individuals with normal circulation	2172/42	♂ 30	130/90	87.9	29.7	18.1	11.5	11.6	6.6	695
	2137/44	♂ 34	132/80	92.8	30.6	13.5	11.0	11.7	7.9	480
	2172/44	♂ 34	138/82	78.2	25.7	16.3	12.6	6.4	6.7	699
	2250/44	♂ 31	114/66	93.4	30.8	14.3	10.8	11.2	7.7	553
	2258/44	♂ 24	118/44	109.7	32.4	14.6	10.7	13.1	8.6	530
	2188/44	♂ 35	110/60	79.8	27.3	9.7	10.7	8.1	9.0	478
	2919/44	♂ 14	118/98	103.4	31.1	15.7	10.1	12.3	8.7	384
	998/44	♂ 32	126/80	72.9	27.1	15.7	11.7	9.5	6.0	619
	2277/45	♂ 34	120/64	74.6	26.3	13.3	12.5	7.7	6.1	702
	2584/45	♂ 20	126/76	106.0	31.7	13.7	10.7	13.9	7.0	596
Aortic Coarctation	M			89.9	29.2	14.5	11.2	10.6	7.4	577
	$\epsilon_M$				$\pm 0.77$	$\pm 0.71$	$\pm 0.26$	$\pm 0.79$	$\pm 0.35$	
	1576/42	♀ 29	190/112	96.9	27.5	20.5	23.6	—4.4	8.4	(524)
	2257/42	♀ 14	164/90	70.2	26.8	17.4	21.3	—3.0	8.5	(503)
	1218/44	♂ 18	194/120	94.2	28.8	17.8	23.2	—4.5	10.1	(446)
	M			87.1	27.7	18.6	22.7	—4.0	9.0	(491)
	$\epsilon_M$				$\pm 0.59$	$\pm 0.94$	$\pm 0.71$	$\pm 0.47$	$\pm 0.55$	

1) that the ascending limb is less steep and the peak of the curve consequently reached after a considerable delay, and

2) that the decline is more constant and gradual — the course of the fall in pressure being represented by a more or less straight line.

For the purpose of studying these characteristics we measured the different time factors in the pulse curves of patients with aortic coarctation and compared them with similar measurements of 10 controls of roughly corresponding ages. The figures of the measurements shown in the tables for each individual case are averages of three consecutive pulses.<sup>1</sup>

The measuring system will be apparent from Fig. 5. Table I gives a description of the distances, and shows the measurements recorded. Table II shows the differences between the distances measured.

#### a d 1. The Gentle Rise of the Femoral Pulse Tracing in Aortic Coarctation.

As will be apparent from Table II, there is a statistically significant difference between the time necessary for the femoral pulse curve to reach its climax ( $B_1$ ) in coarctatic patients, and in normals, viz.,  $11.5 \pm 0.76$  csec.

The interval between the peak of the femoral curve ( $B_1$ ) and the end of the mechanic systole of the heart as shown in the carotid tracing (C) in patients with

<sup>1</sup> Times marked by a Jaquet's chronograph.

aortic coarctation is likewise significantly different from that observable in normals, viz.,  $-14.5 \pm 0.92$  csec. Table I shows how the peak of the femoral pulse curve in normals is always reached before the end of the mechanic systole, and in coarctatic patients, after the termination of the mechanic systole (see reversed order of B<sub>1</sub> and C in Fig. 5). This fact is probably of great diagnostic value and is presumably pathognomic of the malformation in question.

Table II.

Differences.

AC <sub>coarct.</sub> — AC <sub>norm.</sub> = — 1.6 ± 0.97	
AB <sub>coarct.</sub> — AB <sub>norm.</sub> = + 4.1 ± 1.18	t = 7.15
A <sub>1</sub> B <sub>1</sub> <sub>coarct.</sub> — A <sub>1</sub> B <sub>1</sub> <sub>norm.</sub> = + 11.5 ± 0.76	t = 39.2
B <sub>1</sub> C <sub>coarct.</sub> — B <sub>1</sub> C <sub>norm.</sub> = — 14.5 ± 0.92	
AA <sub>1</sub> <sub>coarct.</sub> — AA <sub>1</sub> <sub>norm.</sub> = + 1.6 ± 0.65	

From Table II it will be obvious that there is also a statistically significant difference between the time necessary for the carotid pulse tracing to reach its peak in coarctatic patients and normals, viz.,  $4.1 \pm 1.18$  csec.

#### ad. 2. The Descending Limb in Femoral Pulse Tracings of Patients with Aortic Coarctation.

As will be apparent from Figs. 1—3, the descending limb of the femoral pulse curve in coarctatic patients is more or less a straight line and thereby differs considerably from the corresponding section of the curve of normals (see Fig. 4).

The characteristic feature of the curve of normals is its initial steep decline. This decline is then arrested, or at least checked, by an intervening »secondary peak» caused by the reflection of the pulse wave from the periphery.

Such a secondary elevation cannot occur in aortic coarctation, because the pulse wave is not initiated by a complete stroke volume but by fractions thereof flowing into the aorta at different moments.

Also this is probably pathognomic of aortic coarctation.

The velocity of the pulse wave in the aorta of patients with aortic coarctation is immeasurable, because, as pointed out above, there is no pulse wave in the general conception of the term. Nevertheless in our three cases the delay AA<sub>1</sub> of the »pulse wave» was measured. As will be apparent from Table I, this figure is somewhat higher in coarctatic patients than in normals.

#### Summary.

The carotid and femoral pulse curves of three cases of aortic coarctation were analysed and compared with corresponding curves of 10 controls. The following observations were made:

1) The femoral pulse curve reaches its peak much later in coarctatic patients than in normals, the time necessary being  $22.7 \pm 0.71$  and  $11.2 \pm 0.26$  csec. respectively. The difference is  $11.5 \pm 0.76$  csec.

2) In normals the femoral pulse curve reaches its peak before the end of the mechanic systole of the heart recorded in the carotid pulse curve, whereas in aortic coarctation it is always reached after the end of the mechanic systole. The times are: in coarctatic patients,  $-4.0 \pm 0.47$  csec., and in normals,  $10.6 \pm 0.79$  csec. The difference is  $-14.5 \pm 0.92$  csec.

These changes mentioned under sub-headings 1) and 2) are believed to be of diagnostic value and pathognomic of aortic coarctation.

3) The *carotid* pulse curve also reaches its peak later in coarctatic patients than in normals. The difference is statistically significant  $4.1 \pm 1.18$  csec.

4) The descending limb of the femoral pulse curve in coarctatic patients differs considerably from that in normals. The curve falls more or less gradually and owing to the absence of the reflection of the pulse wave from the periphery of the circulation it contains no secondary peak. These facts are thought to be of diagnostic value.

---

## The Rôle of the Adrenal Cortex and Gonads in the Control of Sexual Hair Distribution.

By

V. K. SUMMERS,<sup>1</sup> M. D., M. R. C. P.,

(Submitted for publication February 22, 1949.)

### Introduction.

The growth of pubic and axillary hair has long been regarded as one of the secondary sex characters, dependent upon the normal maturation and function of the gonads. In recent years, however, the recognition of the importance of the adrenal cortex as a sex gland has thrown doubt on this theory, and considerable evidence has been accumulated suggesting that the control of sexual hair growth is exercised by the adrenal cortex. This investigation was undertaken in an effort to determine the importance of the adrenal cortex and gonads in this respect.

No attempt has been made in this paper to analyse all the factors which may cause loss of sexual hair, *e. g.* senescence and haemochromatosis.

### Castration in the Female.

For the purpose of observing the effects of castration on the sexual hair distribution in the female, it was decided to investigate this problem in a series of women who had undergone the operation of bilateral oophorectomy for endometriosis. In order to allow an adequate time to elapse for the development of any changes which might have been expected to occur, only those patients who had had the operation performed at least five years previously were chosen. As a further safeguard against changes in body hair due to senescence, no patient was observed who was over the age of 40. Thirty-five patients in all were observed and no changes in the distribution of amount of pubic or axillary hair was noticed, compared with the state prior to operation, (Plate 5).

### Castration in Males.

The effects of testicular secretion on the beard, pubic and axillary hair can be observed in those cases in which castration has been performed by trauma or by

<sup>1</sup> 35, Rodney Street, Liverpool, England.



controlling factor in the growth of pubic and axillary hair and reported a case of Addison's disease in a female, in whom axillary and pubic hair were lost. Adler & Abrams (1943) reported a case of Addison's disease in a female in whom pubic and axillary hair was present but scanty; Hadden (1885) noted absence of axillary hair in a case of Addison's disease occurring in a female of 30, but made no comment on the amount or distribution of pubic hair. Rogoff (1942) and Leavitt (1945) both reported cases of Addison's disease in females in whom pubic and axillary hair growth was normal.

In the present study, six cases of Addison's disease occurring in women have been studied; three patients had lost their pubic and axillary hair, one patient had noticed some reduction in the amount of sexual hair and in the remaining two cases no change had been noted. In the three cases in which pubic and axillary hair was lost, the daily excretion of 17-Ketosteroids in the urine was zero. However, no simple relationship exists between the daily excretion of Ketosteroids and sexual hair growth, since in one of the cases in which hair distribution was normal, no 17-Ketosteroids were excreted and in another only 2.5 mg/diem.

Lawrence & Rowe (1929), (Case 3), reported normal sexual hair in a case of Addison's disease occurring in a male of 22, but Weller 1936, (Case 1) noted a feminine distribution of pubic hair in a man of 20. Three cases of Addison's disease in men were studied in the present series. In all cases, sexual hair was abundant, and of masculine distribution. The 17-Ketosteroid excretion in one case was 2.5 mg/diem and in the others 12.5 and 17.3 mg/diem.

### Discussion.

The present study shows that loss of both ovaries in adult life does not cause any alteration in the normal sexual hair growth or distribution. In cases of congenital aplasia of the ovaries, normal sexual hair growth does not occur, (Turner, 1938; Varney, Kenyon & Koch 1942; Albright, Smith & Fraser 1942; Wilkins and Fleischman, 1944). This syndrome is, however, characterised by other congenital abnormalities, *e. g.*, short stature, webbed neck, cubitus valgus, etc., and as in the cases of eunuchoidism in males, the possibility of other endocrine abnormalities cannot be ruled out.

In severe chronic hypopituitarism, loss of pubic and axillary hair is a constant sign. The pathological basis of this syndrome is a destruction of the anterior lobe of the pituitary gland with a consequent loss of its trophic hormones. As a result of this loss of pituitary hormones, atrophy of the suprarenal cortex and particularly the fasciculate and reticulate layers is constantly observed at autopsy (Sheehan & Summers, 1949). Loss of sexual hair in this syndrome might therefore be due to atrophy of the suprarenal cortex rather than to loss of the pituitary gland. If this were so, then destruction of the suprarenal cortex alone should produce similar effects.

Loss of sexual hair in women suffering from Addison's disease is not a constant finding. In some cases a total loss of pubic and axillary hair occurs and this loss appears to occur in those patients in whom the urinary 17-Ketosteroid excretion

approaches zero-values. Additional data are required before this conclusion can be safely drawn, since in Case 7 in the present series sexual hair was normal although no 17-Ketosteroids were excreted in the urine.

Cleghorn (1941) suggested that loss of sexual hair occurred in those cases of Addison's disease caused by atrophy of the adrenal cortex and that the nature of the pathology destroying the cortex was the determining factor. However Case 1 in this series, in which complete loss of sexual hair occurred, was due to bilateral tuberculosis of the adrenals.

Loss of the gonads in men produces alteration in the sexual hair; a feminine distribution of pubic hair results, the beard becomes thinned and axillary hair tends to remain unchanged.

Pan-anterior hypopituitarism, although less common in severe form in men than in women is associated with a loss of pubic, axillary and beard hair. Destruction of the suprarenal cortex in males, severe enough to produce the classical clinical picture of Addison's disease, does not cause loss of sexual hair. The inference is, that the testicular secretions alone are sufficient to maintain the growth of sexual hair.

The adrenal cortex is a source of androgens, oestrogens and progesterone. Administration of testosterone to patients suffering from Simmonds' disease produces a regrowth of pubic and axillary hair (Plate 4); growth of pubic hair has also been reported following the implantation of progesterone in these cases (Simpson 1948). Lisser et al. (1947) reported the successful growth of pubic hair following the administration of Stilboestrol in cases of ovarian aplasia.

The importance of the rôle of the adrenal cortex in maintaining and promoting the growth of sexual hair is clear, since the destruction of the cortex frequently causes a loss of hair and also the administration of steroid hormones, similar to those known to be secreted by the adrenals, produces a growth of pubic and axillary hair.

It is necessary to attempt some explanation of why, in Addison's disease occurring in women, there is not constantly found absence of sexual hair. Such a finding is constant in Simmonds' disease, in which, as previously pointed out, there is atrophy of the fasciculate and reticulate layers of the cortex. In those cases of Addison's disease in women in this series, in which sexual hair was missing and in which autopsy was performed, practically no adrenal cortical tissue was found. Evidence in favour of functional layers in the adrenal cortex has been accumulating during recent years and the suggestion is made that it is the deeper layers of the cortex which are responsible for sex hormone production and for the control of sexual hair growth and distribution.

### Cases.

*Case 1.* F. 43 years. Addison's disease 3 years' duration. Amenorrhoea 2 years. Absent pubic and axillary hair. 17-Ketosteroids 0 mg/diem. Plate 1.

*Case 2.* F. 34 years. Addison's disease 4 years duration. Amenorrhoea. 17-Ketosteroids 0 mg/diem. No pubic or axillary hair. P. M. — Atrophy of suprarenal cortex. No recognisable cortical tissue on the left side; a few scattered cortical cells in right suprarenal.

*Case 3.* F. 43 years. Addison's disease 2 years' duration. Menses regular. 17-Ketosteroids, 6.3 mg/diem. Pubic and axillary hair normal in amount and distribution. *Plate 2.*

*Case 4.* Male 29 years. Addison's disease 3 years' duration. 17-Ketosteroids 2.0 mg/diem. Pubic and axillary hair normal in amount and distribution. *Plate 3.*

*Case 5.* F. 36 years. Addison's disease 1 year. Menses normal. Pubic and axillary hair sparse (patient thought there had been some loss).

*Case 6.* F. 55 years. Addison's disease 1½ years. Menopause 5 years earlier. 17-Ketosteroids 0 mg/diem. Pubic and axillary hair absent.

*Case 7.* F. 41 years. Addison's disease 2½ years. Menses regular. 17-Ketosteroids 0 mg/diem. Pubic and axillary hair present.

*Case 8.* Male 28 years. Addison's disease 6 months. 17-Ketosteroids, 12.5 mg/diem. Pubic and axillary hair normal.

*Case 9.* Male 25 years. Addison's disease 1 year. 17-Ketosteroids 17.3 mg/diem. Pubic and axillary hair normal.

### Summary.

1. The adrenal cortex plays an important part in the control of sex hair distribution.
2. The female gonads play no part in such control in adult life.
3. The male gonads appear to impart the male characteristics to sexual hair distribution.
4. The pathology of the adrenal lesion does not appear to be important in causing loss of sexual hair, but the extent of the destruction appear to be a factor of importance.

I would like to thank Professor H. L. Sheehan and Professor Jeffcoate for their help.

### Literatures.

- Adler, E. H., & Abrams, S. B., 1943, *Am. J. Obst. & Gyn.* 45, 123. — Albright, F., Smith, P. H., & Fraser, R., 1942, *Am. J. M. Sc.* 204, 625. — Capel, E. H., 1923, *Lancet*, ii, 886. — Cleghorn, R. A., 1941, *Anad. M. A.*, 44, 581. — Crooke, A. C., 1937, *Proc. Royal Soc. Med.* 30, 1199. — Foss, G. L., 1937, *Lancet* ii, 1307. — Goldzieher, M. A., 1939, *The Endocrine Glands*, Chap. CXXII, 863. (Appleton & Co. Ltd.) — Hadden, W. B., 1885, *Tr. Path. Soc. Lond.* 36, 436. — Heller, C. G., Nelson, W. O., & Roth, A. A., 1943, *J. Clin. Endocrin.* 3, 573. — Hurxthal, L. M., 1943, *J. Clin. Endocrin.* 3, 551. — Kepler, E. J., Peters, G. A., & Mason, H. L., 1943, *J. Clin. Endocrin.* 3, 496. — Koch, W., 1921, *Ueber d. Russe. Rumanische Kastrateon sekte d. spksen.* — Lawrence, C. H., & Rowe, A. W., 1929, *Endocrinology*, 13, 1. — Leavitt, P., 1945, *New York State Med. J.* 45, 1987. — Lichtenstein, 1919, *Med. Klin.* (876). — Lipshutz, A., 1924, *The Internal Secretions of the Sex Glands* (W. Heffer & Sons). — Lissner, R. H., & Curtis, L. E., 1943, *J. Clin. Endocrin.* 3 (389). — McCullagh, E. P., McCullagh, D. R., & Hicken, N. F., 1933, *Endocrinology*, 17, 49. — Mochlig, R. C., 1940, *Endocrinology*, 27, 743. — Morris, R. T., 1916, *J. A. M. A.*, 47, 741. — Rogoff, J. M., 1942, *J. Clin. Endocrin.* 2, 36. — Rolleston, H. D., 1936, *The Endocrine Glands in Health & Disease*, (Oxford Univ. Press). — Simpson, S. L., 1947, *Discussion of Roy. Soc. Med.* — Sheehan, H. L., Summers, V. K., *Quart. J. Med.*, 1949. — Turner, H. H., 1938, *Endocrinology*, 23, 137. — Weller, G. L., 1936, *Arch. Int. Med.*, 57, 275. — Wilkins, L. and Fleischmann, W., 1944, *J. Clin. Endocrin.* 4, 357. — Zondek, H., 1935, *Disease of the Endocrine Glands*.





Plate I. Case 1. Showing complete absence of axillary and pubic hair in Addison's disease.



Plate II. F. 43 years, showing normal pubic hair growth. Addison's disease. Case No. 3.



Plate III. Male 29 years, showing normal pubic hair growth. Addison's disease. Case No. 4.

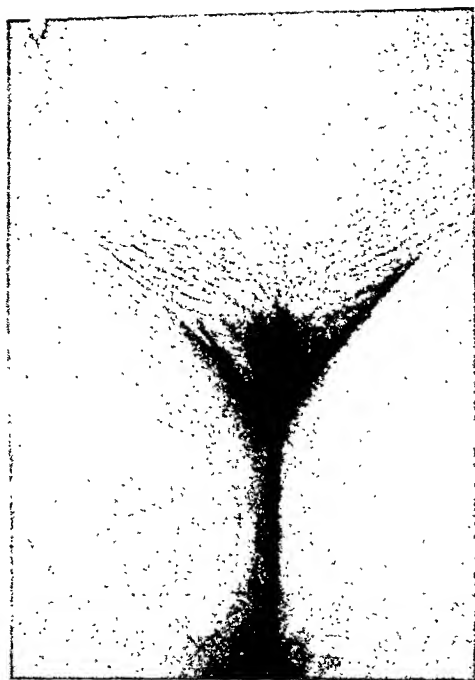


Plate IV. F. 42. Simmonds' disease. Re-growth of pubic hair following administration of testosterone propionate, 50 mg; weekly for 6 months.

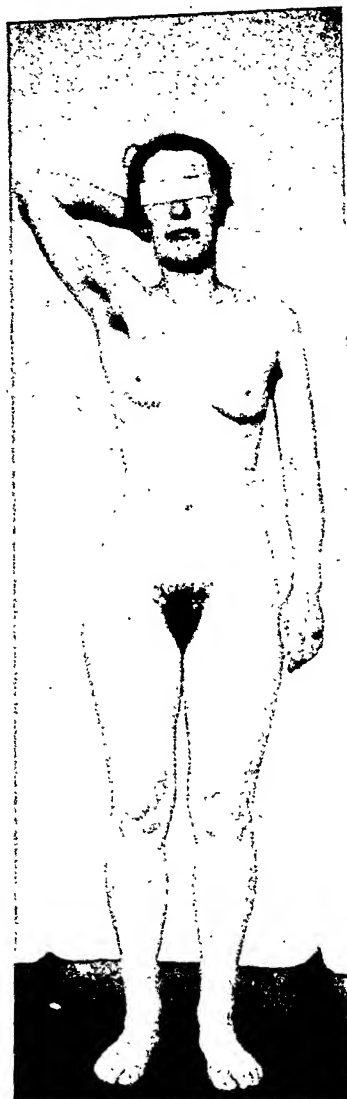


Plate V. F. 44 years. Normal pubic and axillary hair growth, 5 years after bilateral oophorectomy.

From the Medical Departments of the Municipal Hospital, Oslo, Norway.

## The Incidence of Auricular Flutter and Auricular Fibrillation Associated with Complete Auriculo-Ventricular Dissociation.

By

PER HANSSEN, M. D.

(Submitted for publication March 7, 1949.)

---

Several observers (Jourdonais and Mosenthal, Di Gregorio and Crawford, de Moura) have recently drawn attention to the rarity with which complete A—V dissociation is combined with auricular flutter. As far as I can make out, only 30 to 40 such cases have hitherto been published. Among the 72 cases of complete A—V dissociation published by White and Graybiel there was not a single case in which auricular flutter was demonstrated, and there were only 2 cases of auricular fibrillation. In 1945, S. A. Levine wrote:

»On rare occasions true, spontaneous complete heart block with a ventricular rate of 30 may be associated with auricular fibrillation.»

In the same year, P. D. White wrote:

»Auricular fibrillation is a not very rare accompaniment of complete heart block, and auricular flutter has also been noted.»

Certain publications suggest that the rarity with which auricular flutter is associated with complete A—V dissociation is more apparent than real. Thus in 1943, Thorborg stated that in the course of 4 years in a geriatric department he had observed 3 cases of complete A—V dissociation with auricular flutter, and at the same time 4 cases in which A—V dissociation was accompanied by auricular fibrillation. Among the 45 cases of complete A—V dissociation in Fatzer's material there were 2 in which auricular flutter and 9 in which auricular fibrillation was demonstrated. Fatzer does not comment on this remarkably high coincidence rate.

In the period 1936—1945, a total of about 59,000 patients were admitted to the medical side of Oslo's municipal hospitals. Complete A—V dissociation was demonstrated in 66 of these patients. In some of the medical departments electrocardiographic examinations are carried out on all the patients irrespective of

disease and age, whereas in other medical departments such an examination is made only in case of heart disease or of considerable bradycardia or tachycardia. It is most probable that, with only very few exceptions, all the cases of heart block in patients admitted to hospital in the period under review were recognised as such.

During this period the population of Oslo was about 270,000, and it may be assumed that nearly all the patients with total A—V heart block in Oslo were admitted to one or other of the medical departments of the municipal hospitals. The following observations should therefore help to throw light on the frequency of this form of heart disease.

Among the above-mentioned 66 patients there were 7 in whom auricular flutter and 8 in whom auricular fibrillation was demonstrated.

Table 1.

*The distribution according to sex and age of patients with complete A—V dissociation and its frequency in relation to the number of patients treated on the medical side of the hospitals:*

Age	Males	Females
20—39 .....	1	2
40—49 .....	6	4
50—59 .....	7	2
60—69 .....	11	8
70—79 .....	9	9
80— .....	4	3
	38	28
	1: 780	1: 1,060

Table 1 shows that the distribution of all the cases with regard to age and sex coincided with that of the cases already published by other observers.

Table 2.

*The frequency of permanent, intermittent and transitory complete A—V dissociation up to the age of 59 and at the age of 60 and over:*

Age	Permanent		Intermittent		Transitory	
	Males	Females	Males	Females	Males	Females
—59 .....	7	4	5	3	2	1
60— .....	17	14	5	3	2	3
	24	18	10	6	4	4

Table 2 gives the frequency with which permanent, intermittent or transitory heart block occurred as judged by clinical examination and repeated electrocardiographic examinations. The heart block was permanent in 64 per cent., and it was intermittent or transitory in the remainder. Ellis and Fatzer have come to a similar result with regard to the relative frequency of permanent heart block put by the former at 67 per cent., by the latter at 66 per cent. It is probable, and what one should also expect, that intermittent and transitory heart block is relatively more frequent under than over the age of 60.

Among the 66 patients there were 42 in whom various degrees of the Morgagni-Adams-Stokes syndrome, from brief loss of consciousness to death, were demonstrated. White observed this complication in two-thirds of his cases, whereas Fatzer did so only in one-third of his cases. It is not clear why their materials are so different in this respect.

Table 3.

*The number of cases of the Morgagni-Adams-Stokes syndrome in men and women in various age groups:*

Age	Males		Females	
	+	÷	+	÷
20—39 .....	1	0	2	0
40—49 .....	2	4	3	1
50—59 .....	6	1	1	1
60—69 .....	10	1	5	3
70—79 .....	5	4	4	5
80— .....	3	1	0	3
	27	11	15	13

Table 3 shows that the Morgagni-Adams-Stokes syndrome is at any rate just as frequent in the younger as in the older age groups, and is definitely more frequent in men than in women.

White has emphasized the rarity with which angina pectoris and infarct of the heart are associated with complete A—V dissociation. Twelve per cent. of his 117 patients suffering from auriculo-ventricular block suffered from infarct of the heart, and 9 per cent. from angina pectoris. Among 328 patients with clinically infarct of the heart there were only 3.6 per cent. with auriculo-ventricular block, and among 700 patients suffering from angina pectoris there were only 1.5 per cent. with auriculo-ventricular block at the same time. Among my cases were 12 of angina pectoris (18 per cent.), 2 being men under the age of 60, while 5 men and 5 women were over this age. There were also 4 men (6 per cent.) with infarct of the heart. Heart failure, with troublesome dyspnoea on exertion and oedema, was observed in 4 men and 3 women under the age of 60, and in 10 men and 12 women over this age — a total of 29 or 44 per cent. In 27 cases (41 per cent.), neither angina pectoris nor heart failure was observed during the patients' stay in hospital. Table 4 gives a summary of these findings.

Table 4.

*The number of cases of complete A—V dissociation with heart failure, angina pectoris or both these conditions (in the section marked +) compared with the number of cases without these complications (in the section marked ÷).*

Age	Heart Failure		—		Angina pect.	
	Males	÷ Females	Males	÷ Females	Males	÷ Females
—59 .....	7	5	7	3		
60— .....	9	6	15	14		
	16	11	22	17		

Table 5.

*The frequency of the various widths of the QRS waves classified according to sex. The simultaneous occurrence of heart failure or angina pectoris is indicated by the sign +, and the absence of this symptom is indicated by the sign ÷.*

Width of QRS Waves						
Males			Females			
—0.10"	0.11"—0.12"	0.13"—	—0.10"	0.11"—0.12"	0.13"	
÷ 5	4	7	7	3	1	
+ 8	3	11	10	3	4	
13	7	18	17	6	5	

Table 5 shows that heart failure—angina pectoris is not more frequent in patients with widened QRS waves than in those with normal width of the QRS wave. This table also confirms the observation, made by P. D. White among others, that bundle branch block are particularly frequent in men. Among the 23 cases with QRS wave — 0.13" or more, there were 13 cases of left bundle branch block, 4 cases of right bundle branch block, 2 cases of Wilson block, and 4 cases in which there were changes from one type to another of bundle branch block curves.

Bundle branch block (QRS wave — 0.11" or more) was observed in 58 per cent. of White's cases, in 60 per cent. of Fatzer's cases, and in 55 per cent. of my cases. For some unknown reason the corresponding rate in Ellis' material was only 10 per cent.

With regard to the etiology of these conditions, my material does not differ much from that of earlier observers except for the fact that there were no cases of diphtheria in my material which included only one case of complete A—V dissociation due to digitalis.

Table 6.

*The number of cases of auricular flutter or auricular fibrillation observed in association with complete A—V dissociation. Classification according to sex and age:*

Age	Auricular Flutter		Auricular Fibrillation	
	Males	Females	Males	Females
20—39 .....	0	1	0	0
40—49 .....	1	0	1	0
50—59 .....	0	1	2	1
60—69 .....	0	2	0	1
70—79 .....	1	0	2	0
80— .....	1	0	0	1
	3	4	5	3

Among my cases there were 7 in which auricular flutter and 8 in which auricular fibrillation was demonstrated. Table 6 gives the distribution of these cases according to sex and age. It will be noted that there was no sex difference in this respect, and that these conditions seemed to be more frequent in young than in elderly patients.

Table 7 shows the combination of permanent, intermittent and transitory complete A—V dissociation with auricular flutter or auricular fibrillation.

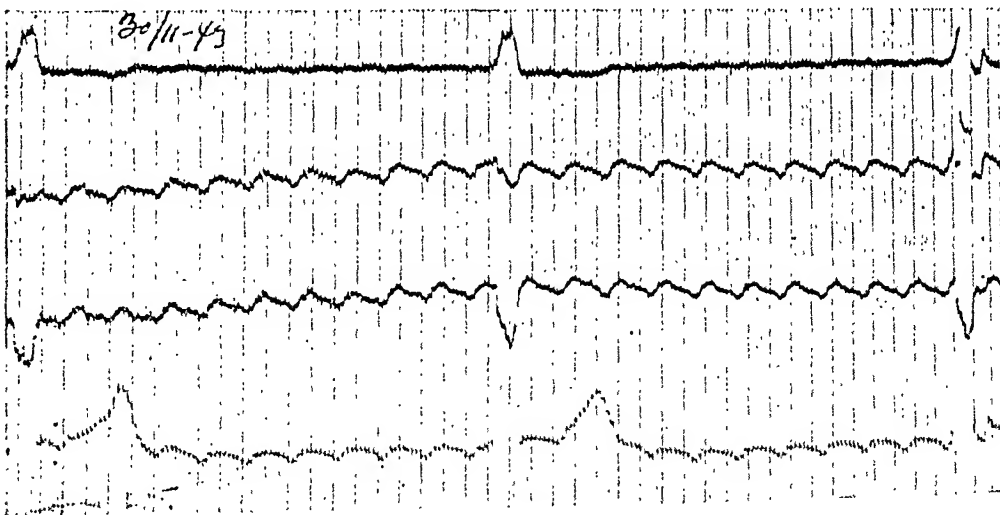
Table 7.

*This table shows the combination of permanent, intermittent or transitory auricular flutter or auricular fibrillation (see text along the axis of the absciss) with at the same time permanent, intermittent or transitory complete A—V dissociation (see text along the axis of the ordinate). The first figures in the various sections give the number of cases of auricular flutter, the second figures the number of cases of auricular fibrillation.*

Complete A—V dissociation	Auricular Flutter — Auricular Fibrillation		
	Permanent	Intermittent	Transitory
Permanent .....	4—4	1—0	2—0
Intermittent .....		0—2	
Transitory .....	0—1		0—1

It is often difficult to distinguish between auricular flutter and auricular fibrillation, and when we have been in doubt, we have preferred the diagnosis of auricular fibrillation to that of auricular flutter.

*Patient nr. 1.* A man, born in 1863, was treated in hospital in 1943, having developed violent precordial pain 2 months before admission. A week before admission loss of consciousness with general convulsions followed by restlessness, repeated attacks of fainting later on. He died during a Morgagni-Adams-Stokes attack. Two electrocardiograms showed complete A—V dissociation. Ventricular rate 32, auricular flutter, rate 300—320, QRS wave 0.14—0.15", partly right bundle branch block, partly left bundle branch block.



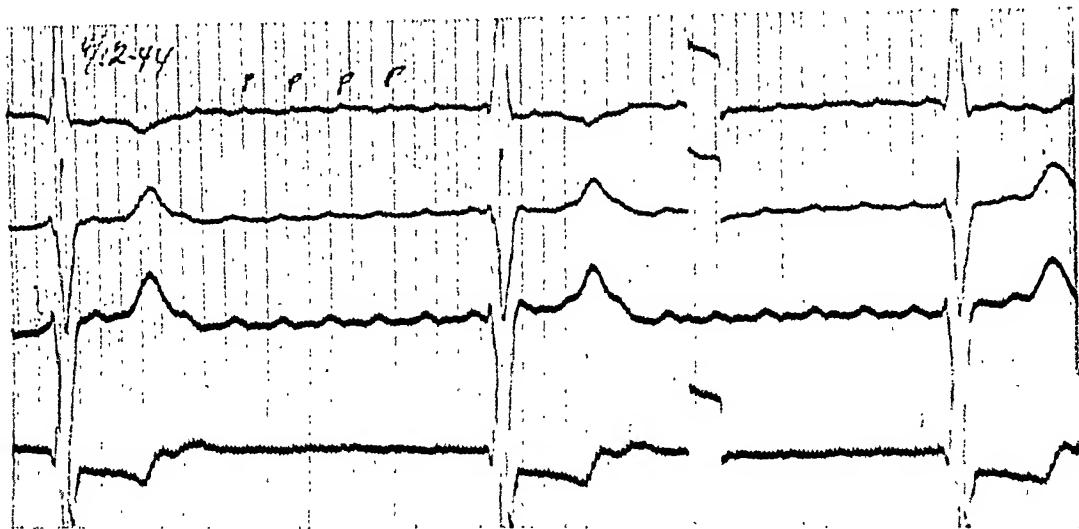
Pas. no. 1. Electrocardiogram (Standard leads + lead  $\overline{\text{IV}}$  R are recorded simultaneously, time record 0.02 second and 0.10 second) showing auricular flutter, rate about 300. Ventricular rate, regular, about 32. Complete A—V dissociation.

*Patient nr. 2.* A woman, born in 1876, contracted rheumatic fever at the age of 15. Angina pectoris since 1945. Treated in hospital 1945—1946. In 1945 an electrocardiogram showed complete A—V dissociation. Ventricular rate 33, auricular flutter, rate 240. A later electrocardiogram showed complete A—V dissociation with auricular rate 80—90.

*Patient nr. 3.* A man, born in 1869, had suffered from dyspnoea on exertion since 1938, and from angina pectoris since 1939. Treated in hospital on several occasions



Pas. no. 2. Electrocardiogram showing auricular flutter, rate about 260. Ventricular rate, regular, about 33. Complete A—V dissociation.

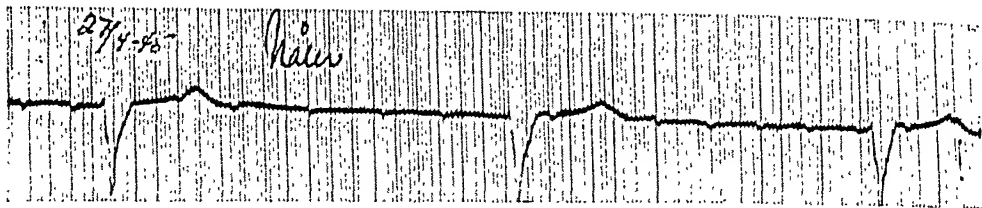


Pas. no. 3. Electrocardiogram showing auricular flutter, rate about 260. Ventricular rate regular, about 28. Complete A—V dissociation.

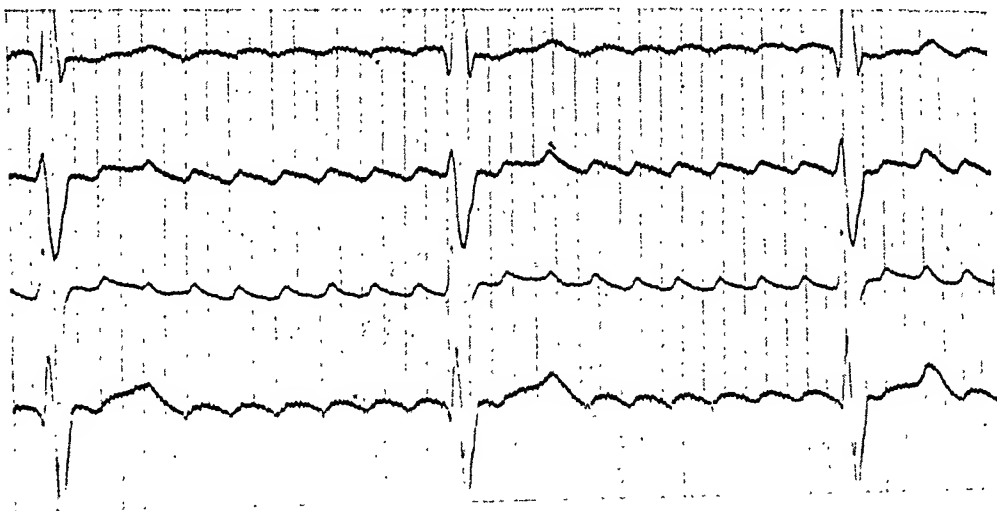
between 1940 and 1946. Since 1940 complete A—V dissociation with regular auricular rate 80—90. Several Morgagni-Adams-Stokes attacks 1941—1942. Since 1944, constant, complete A—V dissociation with auricular flutter, rate 280—320.

*Patient nr. 4.* A woman, born in 1876, suffered from rheumatic fever in 1915 and, since 1942, from considerable dyspnoea on exertion and angina pectoris. Treated in hospital 1942—1944—1945. Between 1942 and 1945, repeated attacks of the Morgagni-Adams-Stokes syndrome. Death from cerebral apoplexy in 1945. No change in the electrocardiogram from 1942 to 1945, — complete A—V dissociation, ventricular rate 32—34, auricular flutter, rate 240.





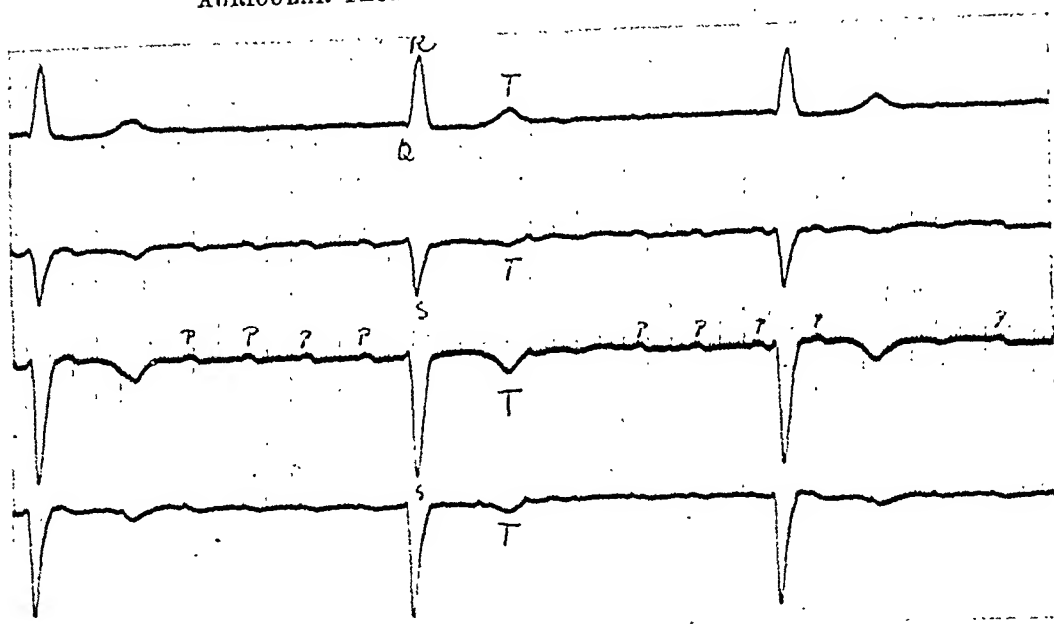
Pas. no. 4. Electrocardiogram obtained with needle electrodes from the region of the second left and right intercostal spaces near the sternum. Auricular flutter, rate about 240. Ventricular rate, a little irregular, rate about 33. Complete A—V dissociation.



Pas. no. 5. Electrocardiogram showing auricular flutter, rate about 300. Ventricular rate, regular, about 32.



Pas. no. 6. Electrocardiogram showing auricular flutter, rate about 400. Ventricular rate, regular about 40.



Pas. no. 7. Electrocardiogram showing auricular flutter, rate about 260. Ventricular rate, regular, about 37.

*Patient nr. 5.* A woman, born in 1903, showed since 1941 complete A—V dissociation with auricular rate 60—80. Treated in hospital 1944—1945. Frequent Morgagni-Adams-Stokes attacks. Considerable dyspnoea on exertion. August—September 1944 complete A—V dissociation with ventricular rate 25—32, auricular flutter, rate 288—300. Since then constant complete A—V dissociation with auricular rate 60—90.

*Patient nr. 6.* A man, born in 1894, had suffered since 1935 from constant bradycardia 30—40. From 1943 to 1946 slight dyspnoea on exertion and slight oedema, and from 1935 to 1946, constant, complete A—V dissociation with ventricular rate 30—40 and auricular flutter, rate about 300. Treated in hospital in 1946.

*Patient nr. 7.* A woman, born in 1892, is the sister of patient nr. 6. In 1935 an electrocardiogram showed sinus rhythm rate 64. PQ—0.30"—0.35". From 1936 to 1942 repeated attacks of fainting, presumably Morgagni-Adams-Stokes attacks. Since 1942 attacks of giddiness only. From 1943 to 1946 electrocardiograms showed complete A—V dissociation with ventricular rate 35—40 and auricular flutter, rate 250.

It will be seen from the illustrations that there was a striking similarity in the electrocardiograms of brother and sister. No definite cause of the heart block was demonstrable in either of them. The possibility that they presented congenital defects of the heart's conduction system, without clinical symptoms till comparatively late in life, cannot be dismissed, although similar observations are not to be found in the literature apart from the cases of congenital heart block in brother and sister described by Aylward.

As auricular flutter and auricular fibrillation are so frequent in my material, it would be interesting to learn if they are of any special prognostic significance. In the common diseases of the heart, auricular flutter and auricular fibrillation are of special significance because they are frequently responsible for considerable tachycardia. With complete A—V dissociation which is nearly always associated with bradycardia, one would expect to find the significance of this complication

to be much less than with the common diseases of the heart. Among the 15 patients suffering from complete A—V dissociation combined with auricular flutter or auricular fibrillation there were only 4 (27 per cent.) who did not suffer from heart failure or angina pectoris, whereas among the rest of the patients there were 23 (45 per cent.) who did not present these conditions.

If we are to judge by these figures, it is possible that heart failure and angina pectoris are more frequent in patients with heart block combined with auricular flutter or auricular fibrillation than they are in patients without these complications.

It is generally agreed that the prognosis for total auriculo-ventricular heart block is bad, but there are certain striking exceptions to this rule among my cases as well as among the cases of all the other observers. The 66 patients treated in hospital in the period 1936—1945 have been traced to the end of 1946, *i. e.* for at least a year and up to 10 years. My cases are too few and the observation period is too short to justify the employment of ordinary statistical methods in calculating the death risk.

Table 8.

*The number of deaths in the various observation years up to the age of 59 and at the age of 60 and over. The figures vertically below the respective observation years give the number of patients under observation in the following year. The figures following immediately after give the number of patients who died in the same observation year.*

		Observation years											
Age		0	1	2	3	4	5	6	7	8	9	10	11
—59 .....	22	3	19	1	18	2	13	0	10	2	7	0	7
60— .....	44	20	24	1	21	1	19	5	11	4	5	2	3

Table 8 gives the deaths in my material as they occurred in the various years of observation. The great number of deaths among persons over the age of 60 during the first year dating from the diagnosis of the disease is very striking. Among the 12 men dying during the first observation year, there were no fewer than 11 who had suffered from the Morgagni-Adams-Stokes syndrome. Among the 11 women who died during the same interval there were only 6 who had suffered from this syndrome.

### Summary.

In the period 1936—1945 and among 59,000 patients admitted to the medical side of Oslo's municipal hospitals there were 66 who were found on clinical and electrocardiographic examination to be suffering from complete A—V dissociation. A comparison with the large materials published by American observers has shown a great similarity of findings with regard to age and sex distribution, the frequency with which the Morgagni-Adams-Stokes syndrome occurred as well as the frequency of permanent and transitory heart block. On the other hand, in the present material there was a remarkably great number of patients who at the same time suffered from auricular flutter (7) or auricular fibrillation (8). This

phenomenon is discussed in some detail with the help of case records and the reproduction of the electrocardiograms of the 7 patients who suffered from auricular flutter. A follow-up study showed among the patients over the age of 60 with complete A—V dissociation there were very many who died during the first year after their disease was diagnosed.

# Literature.

- 1) Aylward, R. D.: Congenital heart-block. *Brit. Med. J.* 1: 943: 1928. — 2) Di Gregorio, N. J. & Crawford, J. H.: Auricular flutter and complete heart block. *Am. Heart J.* 17: 114: 1939. — 3) Ellis, L. B.: Studies in complete heart block, clinical analysis of 43 cases. *Am. J. Med. Sc.* 183: 225: 1932. — 4) Fatzer, G.: Étude de l'électrocardiogramme dans le bloc atrioventriculaire (44 cas). *Cardiologia* 10: 307: 1946. — 5) Jourdonnais, L. F. & Mosenthal, H. O.: Complete auriculoventricular block and auricular flutter with observations of effect of quinidine sulfate. *Am. Heart J.* 14: 735: 1937. — 6) Levine, S. A.: *Clinical Heart Disease*, Third Edition. Philadelphia and London 1945. — 7) De Moura, J. P. P.: Complete auriculoventricular block and bundle branch block with intercurrent auricular flutter. *Am. Heart J.* 32: 794: 1946. — 8) Thorborg, N.: Auricular Flutter and Auricular Fibrillation with complete Auriculo-Ventricular Block. *Acta. Med. Scand.* 114: 507: 1943. — 9) White, P. A. & Graybiel, A.: Complete auriculo-ventricular dissociation, clinical study of 72 cases with note on curious form of auricular arrhythmia frequently observed. *Am. J. Med. Sc.* 192: 334: 1936. — 10) White, P. D.: *Heart Disease*, Third Edition, New York 1945.

From the Medical Department of the University Hospital Bergen, Norway.  
Chief: Professor Håkon Rasmussen. M. D.

## Measurement of the Venous Pressure and of the Circulation Time.

By

OLE STORSTEIN.

(Submitted for publication March 21, 1949.)

During the last 2 years I have measured the venous pressure and the circulation time of as many patients as possible who showed signs of heart disease in the Medical Department of Haukeland Hospital. My objects were to investigate the value of these clinical methods for the functional diagnosis of heart disease and to verify the validity of Nylin's claim that the circulation time depends mainly on the size of the heart. The heart dilates more and more when in failure, and as it increases there is an increase of what Nylin calls the »residual blood», *i. e.* the quantity of blood remaining in the cavity of the heart after the ventricles have emptied their stroke volume into the large arteries. With an increase of the quantity of the »residual blood», dilution of the test substance introduced into the vascular system for the measurement of the circulation time is supposed to occur. This substance becomes mixed with this »residual blood» before it is again pumped out by the heart, and it is in this way that the circulation time becomes prolonged.

The patients were examined according to the technique described by Nylin. A 5 ml Record syringe is filled with 5 ml of decholine and it is connected with a two-way tap and an intravenous needle. The patient lies flat on his back, with one arm abducted about 60 degrees, the bend of his elbow at the level of the mid-axillary line. A substance to be determined by taste, *e. g.* decholine, is injected quickly into a cubital vein, while an assistant with a stop-watch notes the interval between the injection and the moment when the patient first observes a bitter taste in his tongue. The time taken for the taste to disappear is also noted. A vertical glass tube, about 350 mm high, is now connected with the other opening in the two-way tap which is turned so as to connect the needle with the glass tube. The blood rises in it to the level of the venous pressure. The anterior axillary line in the 4th intercostal space is taken as zero. The whole system of tubing with needle is flushed before experiment with a sterile citrate solution. It is well to wait a few minutes before reading off the venous pressure, for it may fall somewhat as the patient

relaxes. In a nervous patient I have seen the venous pressure fall from 250 to 80 mm and in another case from 170 to 60 mm in a few minutes.

The heart volume was radiologically determined in most of the cases according to the method described by Liljestrand, Lysholm, Nylin and Zachrisson. The absolute and the relative volume, *i. e.* the volume per sq.m of body surface were calculated and the vital capacity was also measured in 103 cases.

The circulation rate of the blood in the blood vessels can also be measured directly. Burton-Opitz has found in dogs a circulation rate of 240 mm per sec. in the carotid artery, 1 mm per sec. in the capillaries, and 150 mm per sec. in the jugular vein. This rate, therefore, varies greatly in the different parts of the circulatory system (the rate of circulation of a column of fluid is inversely proportional to its diameter). Such direct measurements have not been made in man, in whom we must determine the circulation time for a greater part of the circulation by the use of substances easily detected when they reach a given point.

In determining the circulation time from a cubital vein to the tongue, magnesium sulphate, saccharine, decholine, sodium cyanide, radium C and radioactive phosphorus may be used. The circulation time from arm to lung can be determined by ether. By subtracting the latter value from the figure indicating the circulation time from arm to tongue, the «crude pulmonary circulation time» is obtained.

When the present investigation was started, 2 ml of a 50 per cent solution of magnesium sulphate were given until decholine could be obtained. This substance, used in a 20 per cent solution, was kindly prepared by Nyegaard & Co.

The normal values obtained by the various methods agree well and average 15 seconds for the time taken between arm and tongue, the extreme limits being 10 and 20 seconds. The circulation time between arm and lung, measured by ether, is 4 to 8 seconds.

Moritz & Tabora have found that the normal venous pressure ranges from 10 to 90 mm. Winsor & Burch found normal values ranging from 50 to 140 mm of water taking the mid-axillary line as zero, but Warburg, taking the anterior axillary line as 0, has found the upper limit for the normal venous pressure to be 115 mm of blood.

These methods of examination can be applied to *clinical diagnosis*. By measuring the venous pressure we can distinguish between enlargement of the liver and oedema of cardiac origin on the one hand, and other conditions such as cirrhosis of the liver and enlargement of the liver with ascites due to malignant growths on the other hand.

Measurement of the venous pressure may help in the diagnosis of constrictive pericarditis. In a patient with oedema, enlargement of the liver and ascites, but with a heart of normal size and without radiological evidence of earlier pericarditis, repeated measurements of the venous pressure, yielding figures of about 200 mm, enabled us to make the correct diagnosis of constrictive pericarditis. In cases of acute pericarditis a rising venous pressure is a guide to cardiac tamponade and calls for paracentesis.

A marked rise of the venous pressure has been observed in cases of local obstruction to the circulation of blood in the region of the superior vena cava. A pa-

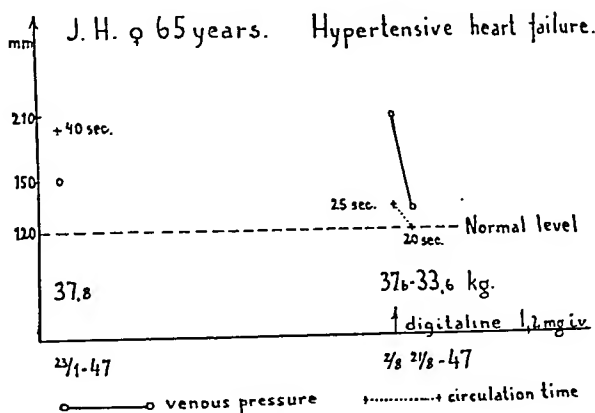
tient with thrombosis of the superior vena cava and Stokes collar had a venous pressure in the right arm of 180 mm and in the left arm of 265 mm. A patient with traumatic thrombosis of the axillary vein had a venous pressure of 180 mm in the affected arm.

Measurement of the circulation time may help us to distinguish between diseases of the heart and lungs. In several cases of bronchial asthma a normal circulation time between arm and tongue was found.

In a case of auricular septal defect, the circulation time was found to be as short as 7 seconds. This observation suggested shunting of blood from the right to the left side of the heart.

In the *functional diagnosis* of diseases of the heart, measurements of the venous pressure and of the circulation time may give us clues to the degree of failure.

Fig. 1



Repeated measurements are also a guide to assess improvement or deterioration in the patient's condition and provide objective data with which the effect of treatment may be estimated.

The first patient (fig. 1), a woman of 65 years, suffered from hypertensive heart disease. During her stay in hospital in January 1947 she was in congestive failure with dyspnoea, oedema and enlargement of the liver. At that time her venous pressure was 150 mm, and her circulation time was 40—85 seconds, measured with magnesium sulphate. With rest in bed, reduction of salt in the diet and digitalis, her weight fell from 39.5 to 36.5 kg, and when she was discharged as a walking patient there was no oedema. She returned to hospital in July of the same year with considerable congestive failure. Her venous pressure was now 210 mm, and her circulation time was 25—60 seconds, measured with decholine. She was treated with digitalis (a single dose of Digitaline Nativelle of 1.2 mg). Her weight fell by 4 kg in 5 days, her venous pressure fell to 120 mm, and her circulation time to 20—35 seconds.

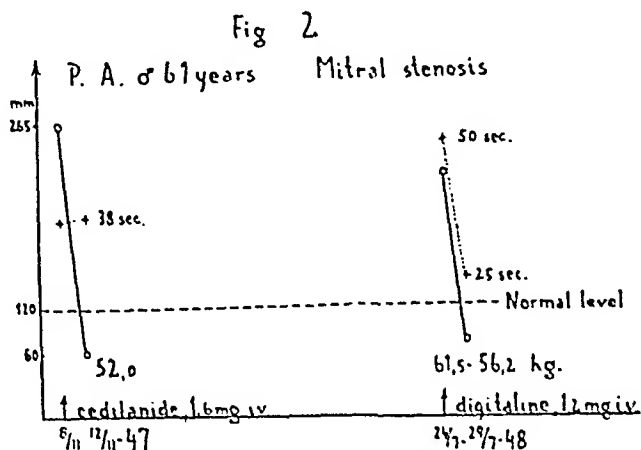
The second patient (fig. 2), a man of 61 years, suffered from rheumatic heart disease and signs of congestive failure during the last three years. On admission to hospital on November 8, 1947, he was exhausted and cyanosed and suffered from severe dyspnoea and oedema. With intravenous digitalis (Cedilamide 1.6 mg) his venous pressure fell in four days from 265 to 60 mm. His circulation time remained more or less unchanged (37—72, 38—93 seconds). His weight fell gradually to 52 kg. When re-admitted on July

23, 1948, he had not taken digitalis recently. He was now in a state of severe congestive failure. After the intravenous administration of 1.2 mg Digitaline Nativelle, his venous pressure fell in 5 days from 220 to 55 mm, his circulation time from 50—90 to 25—65 seconds, and his weight from 61.5 to 56.2 kg.

The present series consists of 444 patients and 23 healthy persons acting as controls. The cases were divided into the following groups according to clinical standards:

I. *Compensated cases*: Patients without signs of heart failure. They would belong to the Groups 1 or 2 according to the classification of the New York Heart Association.

II. *Uncompensated cases*: These patient would be placed in Groups 3 or 4 of the same classification. They belong to one or other of the following sub-groups:



*Right-sided, left-sided and combined right- and left-sided heart failure.* This division is determined by the clinical signs which were most prominent: right-sided heart failure was diagnosed when there was congestion in the systemic circulation, venous congestion in the neck, enlargement of the liver and oedema. Left-sided heart failure was diagnosed when there were signs of congestion of pulmonary circulation with dyspnoea in its various forms, ranging from dyspnoea on exertion to dyspnoea with oedema and congestion of the lungs and a productive cough. I have attempted to make this classification as independent as possible of the results obtained from measurements of the venous pressure and the circulation time.

Table I shows the *results*. The average normal figure for venous pressure was found to be 77 mm, with extremes of 25 and 120 mm. The circulation time with decholine was on the average 13.7 seconds, the extremes being 7 and 20 seconds at the first sign of taste. The average for the disappearance of taste was 26.6 seconds, the extremes being 14 and 36 seconds.

The *venous pressure* was found to be normal in cases of compensated heart disease and in patients with signs of purely left-sided heart failure. The venous pressure was considerably raised in cases of right-sided heart failure and when right- and left-sided heart failure were combined. The venous pressure was somewhat higher



Table I.

<i>Compensated heart disease</i>		Number	M $\pm$ $\epsilon$ M	$\sigma \pm \sigma_M$	$\sigma\%$
Venous pressure in mm .....		238	87.5 $\pm$ 1.4	31.4 $\pm$ 1.4	35.9
Circulation time (mag.sulph. I).....		76	13.8 $\pm$ 0.76	6.6 $\pm$ 0.54	47.8
» » ( » II).....		74	66.2 $\pm$ 3.7	32.0 $\pm$ 2.6	48.5
» » (decholine I).....		131	14.6 $\pm$ 0.44	5.0 $\pm$ 0.31	34.2
» » ( » II).....		127	33.4 $\pm$ 1.1	12.4 $\pm$ 0.78	37.1
Heart volume (V) ml .....		188	772.9 $\pm$ 17.4	238.5 $\pm$ 12.3	30.9
» » per Sq.m (V/M <sup>2</sup> ) .....		183	442.2 $\pm$ 9.2	124.4 $\pm$ 6.5	28.1
<i>Right-sided heart failure</i>					
Venous pressure in mm .....		16	177.5 $\pm$ 14.6	58.4 $\pm$ 10.3	32.9
Circulation time (mag.sulph. I).....		6	16.8 $\pm$ 2.7	6.54	38.9
» » ( » II).....		4	75.8 $\pm$ 15.0	29.9	39.5
» » (decholine I).....		10	15.9 $\pm$ 1.5	4.7	29.6
» » ( » II).....		6	33.2 $\pm$ 4.6	11.2	33.9
Heart volume (V) ml .....		12	945.0 $\pm$ 65.3	226.0	23.9
» » per Sq.m (V/M <sup>2</sup> ) .....		12	515.4 $\pm$ 35.5	123.1	23.9
<i>Left-sided heart failure</i>					
Venous pressure in mm .....		76	93.3 $\pm$ 3.51	30.6 $\pm$ 2.48	32.8
Circulation time (mag.sulph. I).....		18	24.4 $\pm$ 2.7	11.3 $\pm$ 1.9	46.3
» » ( » II).....		18	91.1 $\pm$ 6.2	26.5 $\pm$ 4.4	29.1
» » (decholine I).....		45	23.3 $\pm$ 1.1	7.1 $\pm$ 0.7	30.5
» » ( » II).....		44	49.3 $\pm$ 2.7	18.0 $\pm$ 1.9	36.5
Heart volume (V) ml .....		51	1,177.5 $\pm$ 45.9	237.8 $\pm$ 32.5	27.8
» » per Sq.m (V/M <sup>2</sup> ) .....		50	698.0 $\pm$ 26.9	190.0 $\pm$ 19.0	27.2
<i>Right- and left-sided heart failure</i>					
Venous pressure in mm .....		86	161.6 $\pm$ 6.43	59.6 $\pm$ 4.55	37.0
Circulation time (mag.sulph. I).....		16	35.0 $\pm$ 6.0	24.0 $\pm$ 4.2	68.6
» » ( » II).....		16	137.5 $\pm$ 17.8	71.3 $\pm$ 12.6	51.9
» » (decholine I).....		64	30.0 $\pm$ 1.8	14.4 $\pm$ 1.3	48.0
» » ( » II).....		62	64.5 $\pm$ 5.5	43.4 $\pm$ 3.9	67.3
Heart volume (V) ml .....		42	1,373.8 $\pm$ 55.0	356.4 $\pm$ 38.9	25.9
» » per Sq.m (V/M <sup>2</sup> ) .....		42	900.0 $\pm$ 33.4	216.3 $\pm$ 23.6	24.0
<i>Controls</i>					
Venous pressure in mm .....		23	77.0 $\pm$ 4.12	19.8 $\pm$ 2.98	25.7
Circulation time (decholine I).....		19	13.0 $\pm$ 0.77	3.4 $\pm$ 0.55	24.8
» » ( » II).....		18	26.6 $\pm$ 1.34	5.7 $\pm$ 0.95	21.4
<i>Graves' disease</i>					
Venous pressure in mm .....		26	88.25 $\pm$ 7.0	35.6 $\pm$ 4.94	40.0
Circulation time (decholine I).....		27	11.8 $\pm$ 0.98	5.08 $\pm$ 0.69	43.0/
» » ( » II).....		25	25.5 $\pm$ 2.02	10.01 $\pm$ 1.43	39.6
Heart volume (V) ml .....		28	609.0 $\pm$ 31.4	167.5 $\pm$ 22.4	27.5
» » per Sq.m (V/M <sup>2</sup> ) .....		28	366.0 $\pm$ 18.9	100.0 $\pm$ 13.4	27.3

in cases of pure, right-sided heart failure. These findings might be expected on the evidence of the clinical picture.

The estimations of the *circulation time* with magnesium sulphate and with decholine conformed well with regard to the first readings, but for the last readings

the sensation of heat lasted considerably longer with magnesium sulphate than the time taken for the taste of decholine to disappear. With both methods the circulation time was found to be normal in cases of compensated heart disease and of pure right-sided heart failure. It was considerably prolonged in cases of left-sided heart failure, and was highest in combined right- and left-sided heart failure.

The *heart volume*, as determined radiologically, was normal in the compensated cases, the upper limit for the relative volume being 450 ml per sq.m of body surface for women and 500 ml for men (Nylin). In cases of right-sided heart failure there was an insignificant increase of the relative volume, whereas this increase was considerable in cases of left-sided heart failure, and very marked (to nearly twice the normal) in combined heart failure.

Table II.

Correlation	Number	$r \pm \epsilon r$
<i>Compensated heart disease</i>		
Volume/M2 — circulation time .....	174	$0.333 \pm 0.068$
Volume/M2 — venous pressure .....	179	$0.02 \pm 0.075$
<i>Incompensated heart disease</i>		
Volume/M2 — circulation time .....	86	$0.18 \pm 0.18$
Volume/M2 — venous pressure .....	103	$0.10 \pm 0.097$
Vital capacity — circulation time .....	103	$\div 0.27 \pm 0.092$
Vital capacity — volume/M2 .....	79	$\div 0.235 \pm 0.107$

### Discussion.

Nylin calculated the correlation coefficient for some of his readings. He found good agreement between the relative heart volume and the circulation time on the first reading in cases of compensated heart disease. In uncompensated cases this agreement was not so good. But Nylin states that this supports his theory that the circulation time depends first and foremost on the size of the »residual blood» *i. e.* the volume of the heart. It seems to me that we can attach no importance to the very small correlation coefficients in Nylin's material — 0.50 and 0.37 respectively.

In table II I have tried to correlate some of the readings from my cases. The best correlation is obtained between the relative heart volume and the first reading of the circulation time, in compensated cases, but the correlation coefficient is here only 0.33. The correlation between the relative heart volume and the circulation time in uncompensated cases, and the relative heart volume and the venous pressure in compensated and uncompensated cases is not reliable. The correlation coefficient for vital capacity to circulation time and for vital capacity to relative heart volume is negative, indicating an inverse ratio. But the correlation is not significant enough for any of these readings.

Thus the calculation of the correlation for some of my readings gives no indication why the circulation time is prolonged or the venous pressure raised. Table I shows, as expected, a raised venous pressure in cases of right-sided heart failure.

The venous pressure was highest in the group of pure right-sided heart failure, which included a certain number of patients with impaired inflow to the heart, with acute or chronic constrictive pericarditis. The circulation time was prolonged in cases of pure left-sided heart failure, whereas it was normal in cases of pure right-sided heart failure. It is therefore clear that the congestion in the lungs is responsible for the prolongation of the circulation time. This has already been demonstrated by Hitzig, King and Fishberg, who, working with saccharine, found the circulation time prolonged in 30 of their 31 cases of pure left-sided heart failure. Bedford has investigated 154 cases of pure left-sided heart failure with the help of decholine, and found considerable prolongation of the circulation time from arm to tongue, whereas the circulation time from arm to lung was normal with ether. He has therefore shown that there is a prolongation of the circulation time in the lung itself which is characteristic of left sided heart failure. Levine maintains that it is particularly in cases of chronic congestion of the lungs that we find prolongation of the circulation time indicating failure of the left ventricle.

Table I shows a remarkably short circulation time in Graves' disease in which the venous pressure, on the other hand, was normal. These cases included some with uncompensated heart disease due to hyperthyreoidism, and in these cases also the circulation time was normal. Though Levine made the same observation earlier, it seems to me to have attracted little attention as an aid to differential diagnosis in heart disease due to hyperthyreoidism. In cardiac insufficiency, the differential diagnosis from mitral stenosis may be difficult even with the help of auscultation as well as radiological examination. If Fishberg's formula for the connection between cardiac output and circulation time is correct (an inverse proportion of the one factor to the other) it supports Mc Michael's opinion of thyrotoxic heart disease as a »high output failure», *i. e.* heart failure with increased cardiac output, such as is also found in anaemia, beri-beri, arteriovenous aneurysm, Paget's disease and cor pulmonale. In contrast to this, we find the ordinary »low output failures» with diminished cardiac output — hypertensive, rheumatic, arteriosclerotic and syphilitic diseases of the heart.

### Summary.

In a series consisting of 238 compensated and 178 uncompensated patients with heart disease, 23 healthy persons, and 28 patients with Graves' disease, measurements were made of the venous pressure and the circulation time, the volume of the heart being determined by radiological examination. The vital capacity of 103 of these patients were also measured.

Calculations with a view to a correlation between some of the figures obtained failed to confirm Nylin's claim that the circulation time depends mainly on the size of the heart. It was found that the circulation time was prolonged mainly in cases of left-sided heart failure, whereas the venous pressure was raised in cases of failure of the right ventricle.

Measurements of the venous pressure and the circulation time can give us

valuable information for the diagnosis of diseases of the heart and lungs and provide a useful index to improvement or deterioration in the patient's condition, and to the effects of treatment.

#### Literature.

Bedford, D. E.: *Lancet* 1939: 236: 1303. — Burton-Opitz cit. Fishberg. — Fishberg, A. M.: *Heart Failure*. Philadelphia 1940. — Gernandt, B. and Nylin, G.: *Nord. Med.* 1946: 30: 1386. — Hitzig, King and Fishberg cit. Fishberg. — Levine, S. A.: *Clinical heart disease*. Philadelphia 1945. — Liljestrand, G., Lysholm, E., Nylin, G. and Zachrisson, C. G.: *Am. Heart Journ.* 1939: 17: 406. — McMichael, J.: *Quart. Journ. Med.* 1944: 37: 123. — Moritz and Tabora cit. Fishberg. — Nylin, G.: *Nord. Med.* 1945: 26: 1033. — Warburg, E.: *Nordisk Lærebog i Intern Medicin Bd. IV*. Kobenhavn 1943. — Winsor, T. and Burch, G. E.: *Am. Heart Journ.* 1946: 31: 387.

---

Travail de la 11<sup>ème</sup> Clinique médicale de l'Université Charles IV à Prague.  
(Directeur: Professeur Dr. Kristian Hynek.)

## Sur l'élimination urinaire de la quinine dans les hépatopathies.

Par

VOJTĚCH HOENIG.

(Ce travail est parvenu à la rédaction le 3 Mars, 1949.)

Beaucoup d'auteurs ont étudié à l'aide de la quinine (q.) le pouvoir de détoxication du foie (Händel, Weill, Hinrichs, Miano, Duperie et collab., Montero, Castello, Pallardo, Lebon etc.). Après administration perorale d'une certaine quantité de q., ils ont suivi qualitativement la quininurie à l'aide du réactif de Tanret. Dans les cas manifestes ou supposés de lésions diffuses du foie une hyperquininurie s'est révélée dans les premières heures après l'administration de la q., tandis que chez les sujets sains l'élimination a été nulle ou minime.

Étant donné qu'à notre clinique les résultats de cette épreuve n'ont pas correspondu à ceux des auteurs précités (Štork), nous avons entrepris, profitant du pouvoir fluorescent de la q. en solution, une étude quantitative de la question.<sup>1</sup>

### Méthode.

A 6 h. du matin vider la vessie et administrer 0.20 gr de sulfate de q. per os avec 100 ml de liquide. Boire 250 ml de liquide à 8, 10, 12 et 15 heures. Collecter et mesurer l'urine de 8 à 18 heures, toutes les deux heures, l'urine totale de 18 à 18 heures le lendemain et de 18 à 18 heures le surlendemain. Boucher et mettre à l'obscurité les échantillons de chaque portion.

Faire digérer pendant 30 min. 10 ml d'urine par 90 ml de NaOH à 2 %. Compléter ensuite à 200 ml par de l'eau dist. Effectuer l'extraction de la q. par du chloroforme et de l'acide sulfurique 0.1 n., pendant 15 et 10 min. respectivement dans les extracteurs décrits par Kyker et collab. Déterminer la concentration de la q. par comparaison de la valeur lue au fluorophotomètre de Pfaltz et Bauer avec la courbe de calibration qui est une droite. Calculer la quininurie.

<sup>1</sup> Nous remercions Monsieur le Professeur Hořejší pour les conseils précieux qu'il nous a donnés, Madame Válková et Monsieur le Docteur Berman pour leur aide technique au cours du travail.

Les résultats sont rapportés sur les tableaux, courbes et graphiques moyens.

Nous avons suivi de cette façon là 47 sujets en tout:

10	sujets jeunes	(âge moyen 24 ans)	sans lésion hépatique manifeste,
8	» plus âgés	( » » 56 » )	» » » » ,
7	» jeunes	( » » 29 » )	avec lésion aiguë du foie,
9	» plus âgés	( » » 47 » )	» » » » ,
13	» cirrhotiques	( » » 55 » )	.

L'élimination a été suivie chez 40 sujets pendant 12 heures et chez 27 sujets pendant 60 heures, dont certains des 40 précités.

### Résultats.

Voir tab. 1, 2, 3 et fig. 1, 2, 3.

### Discussion.

En comparant les résultats obtenus nous voyons que:

1) la quinurie est maximale pendant les premières heures chez les sujets jeunes sans lésion hépatique;

2) elle est légèrement retardée et basse au début chez les sujets âgés sans lésion hépatique;

3) elle est retardée, prolongée et basse au début chez les hépatiques aussi bien aigus que chroniques;

4) la diurèse va très souvent parallèlement avec la quinurie;

5) l'élimination de la q. en 60 heures est approximativement égale dans tous les groupes; elle paraît être légèrement augmentée chez les cirrhotiques;

6) la diurèse en 60 heures est à peu près égale dans tous les cas sauf chez les cirrhotiques où elle paraît être inférieure.

Il s'en suit que l'élimination de la q. chez les hépatiques et les sujets âgés n'est pas diminuée, comme on pourrait le croire d'après les fig. 1 et 2; elle est seulement retardée. Pourquoi ce retard?

La q. peut s'arrêter ou se perdre pendant le passage métabolique: 1. dans l'intestin, 2. dans le sang, 3. dans les tissus, 4. dans les reins.

La première possibilité pourrait entrer en ligne de compte dans les cas de cirrhoses avancées avec vénostase gastrointestinale prononcée et par là avec troubles de résorption. La q. pourrait se perdre aussi dans les selles diarrhéiques; nous avons éliminé ces derniers cas. Quant à la deuxième possibilité, le retard dans le sang est peu probable. Hiatt et collab. ont trouvé une concentration faible dans les érythrocytes et nous mêmes avons constaté un abaissement rapide du taux sanguin de la q. après injection intraveineuse. Il reste les tissus (foie, poumons, rate, peau et reins). La q. qui pénètre du sang portal et artériel dans les tissus y est détruite (70 à 80 % d'après Moller) dans le système réticulo-endothélial, par un ferment appelé quinine-oxydase (Ramsden et collab., Anderson et collab.). Le reste, qui varie beaucoup (Baur et autres), est éliminé par les reins où une partie est réabsorbée (Haag et collab.).

Dans les tissus la q. peut être retenue par le SRE (Boecker, Giemsa, Chen et Geiling et autres) et dans le système lacunaire. Ce dernier système colloïdal complexe joue un rôle important dans le métabolisme de l'eau et des substances minérales. On sait que les hépatopathies aiguës et chroniques présentent des troubles de ce dernier, en premier lieu rétention du liquide. La même chose s'est trouvée être vraie pour les sujets âgés comme l'a constaté Trojan chez nous.

A la base de tout cela nous sommes en droit de penser que l'élimination urinaire de la q. dépend en premier lieu de sa dégradation tissulaire et de l'échange hydrique. D'autres facteurs, comme par exemple le pH urinaire (Haag et collab.) jouent un rôle secondaire.

Notre idée est soutenue par le fait que 1) la quinurie est souvent parallèle avec la diurèse, 2) la diurèse provoquée chez les cirrhotiques par les diurétiques mercuriels (fig. 4) augmente la quinurie, 3) la diurèse en 60 heures est comme la quantité de la q., approximativement égale dans tous les groupes.

L'intensité de dégradation et les propriétés colloïdales du système lacunaire sont des facteurs qui changent d'un sujet à l'autre et d'un moment à l'autre. C'est ainsi que nous pouvons comprendre notre constatation que la quinurie, quoique augmentée par la diurèse provoquée (fig. 4) n'est pas proportionnelle à celle-ci; que la quinurie n'est pas toujours parallèle à la diurèse normale.

La quantité plus élevée de q. éliminée en 60 heures chez les cirrhotiques pourrait s'expliquer par la présence d'une circulation collatérale abdominale et de ce fait par l'exclusion d'une partie du système réticuloendothélial. Mais le nombre relativement peu élevé de cas ne nous permet pas de voir, par application de règles de statistique, si cette quantité ne se trouve pas encore dans les limites d'erreur.

Pour terminer il faut donc souligner qu'il n'y a pas d'hyperquinurie chez les hépatiques. Celle-ci serait due, d'après les auteurs proposant l'épreuve à la q., à l'activité affaiblie de la quinine-oxydase dans le foie malade. Kelsey et collab. ont cependant démontré que le foie humain en contient une quantité minime. Ceci confirme notre idée que l'activité de la quinine-oxydase n'est pas touchée dans les hépatopathies.

### Summary.

1) The quinuria has been quantitatively studied in 47 persons after peroral administration of 0.20 grams of quinine sulfate.

2) A retardation in the elimination was found both in acute and chronic liver disease and old people with normal liver.

3) The amount excreted in 60 hours did not differ notably in persons with liver disease and without.

4) The quinuria runs often parallel with the diuresis.

5) There is probably a relation between the quinine elimination and the water metabolism.

6) The retardation in the quinine elimination in liver diseases and in older people may be related to the trouble of the water metabolism.

## Bibliographie.

Anderson, C. E., et Andrews, J. C.: *Fed. Proc.*, 1: 97, 1942. — Baur, H.: *Helvet. med. acta*, 15: 499, 1948. — Boecker, E.: *Arch. exper. Path. (allem.)*, 99: 200, 1923. — Castello, A., et Ruiz, S.: *Med. españ.*, 13: 219, 1945. — Chen, G., et Geiling, E. M. K.: *J. Pharmacol.* 82: 120, 1944. — Christen, W.: *Z. klin. Med.*, 133: 563, 1938. — Cushny, A. R., Grollman, A., et Slaughter, D.: *Pharmacology and therapeutics*, Londres, 1947. — Giemsa, G.: *Münch. med. Wschr.*, 74: 574, 1927. — Haag, H. B., Larson, P. S., et Schwartz, J. J.: *J. Pharmacol.*, 79: 136, 1943. — Haendel, M.: *Z. exper. Med.*, 47: 145, 1924. — Hartmann, H., et Zila, L.: *Arch. exper. Pathol.*, 83: 221, 1918. — Hiatt, E. P., et Quinn, G. P.: *J. Pharmacol.* 83: 101, 1945 (C. r. dans *Chem. Abstr.*, 39: 2934, 1945). — Hinrichs: *Zbl. inn. Med.*, 785, 1939. — Hoenig, V., et Berman, J.: *Čas. lék. česk.*, 87: 1122, 1948. — Hoenig, V.: *Čas. lék. česk.*, 88: 91, 1949. — Horejsí, J.: *Maladies du foie (en tchèque)*, Prague, 1947. — Kelsey, F. E., et Oldham, F. K.: *J. Pharmacol.*, 79: 77, 1943. — Kyker, G. C., Mc Ewen, M. M., et Hill, Ch.: *J. Labor. a. Clin. Med.*, 32: 196, 1948. — Lebon, J., Choussat, Nouredine: *Algérie méd.*, 1, 1946, (cité dans la *Presse méd.* 712, 1946). — Miano, S.: *Rif. med.*, 56: 35, 1940. — Moller, K. O.: *Pharmakologie*, Bâle, 1947. — Montero, A.: *Gac. med. españ.*, 18: 368, 1944. — Pallardo, L. F.: *Sem. méd.*, 54: 721, 1947. — Pelnář, J.: *Pathologie et thérapeutique des maladies internes (en tchèque)* Prague, 1947. — Prusík, B., et Herles, F.: *Čas. lék. česk.*, 1051, 1947. — Ramsden, W., Lipkin, I. J. et Whitley, E.: cité par Anderson. — Štok, A.: d'après communication personnelle. — Trojan, A.: d'après communication personnelle. — Turon, M.: *Presse méd.*, 803, 1946. — Vančura, A.: *Čas. lék. česk.*, 766 et 1223, 1929; 1113, 1931. — Weill, O., et Le Cluisse, R.: cité par Baur.

---



Table 1.

*Sujets jeunes et âgés sans lésion hépatique.*

Quininurie en mg et diurèse en ml de 6 à 18 h. Les 3 dernières colonnes: élimination de la q. et diurèse totale dans les 12 premières heures et les 48 heures suivantes.

A. Sujets jeunes; on constate une large variation de la quininurie et de la diurèse. Cependant le maximum d'élimination dans les premières 6 heures est net.

B. Sujets âgés; variation moins large; valeurs élevées exceptionnelles.

sex, âge, diagn.	6-8 h.		8-10 h.		10-12 h.		12-14 h.		14-16 h.		16-18 h.		6-18 h.		18-18 h.		18-18 h.	
	quinine	diurèse	quinine	diurèse	quinine	diurèse	quinine	diurèse	quinine	diurèse	quinine	diurèse	quinine	diurèse	quinine	diurèse	quinine	diurèse
A.																		
♂ 17 a. rhumatisme..	3.65	100	6.42	147	6.10	167	2.29	130	1.61	86	2.94	100	23.01	730				
♂ 27 a. endocardite..	0.93	80	4.00	105	3.24	130	3.38	100	2.03	60	1.57	86	15.15	561				
♀ 22 a. tbc. fibreuse.	1.64	30	3.20	175	1.03	30	1.33	32	1.04	39	1.99	48	10.33	354	6.70	550		
♂ 26 a. st. p. pneum.	2.23	106	2.89	152	2.36	126	1.62	136	1.98	100	1.25	105	12.33	725	9.68	1,100		
♀ 21 a. norm. ....	0.84	42	3.30	375	4.07	220	4.88	192	1.10	105	3.66	330	17.85	1,264	5.37	420	13.00	1,000
♂ 29 a. asthme. ....	2.30	82	2.94	100	2.53	109	2.17	178	2.00	200	2.33	210	14.27	879	6.20	380	3.40	540
♂ 21 a. purpura. ....	3.60	90	4.19	108	4.14	234	3.32	120	5.42	116	4.67	255	25.34	923	6.12	850	3.60	900
♀ 27 a. tbc. pulm. ...	2.27	50	2.65	90	2.92	85	2.54	100	1.27	68	2.40	160	14.05	553	4.66	530	5.00	950
♀ 26 a. amyg. chr. ...	0.66	100	1.62	195	2.11	320	1.41	150	1.37	130	1.67	190	8.84	1,085	15.00	1,500	11.00	1,850
♀ 18 a. cholelithiase.	4.00	165	4.61	185	3.44	215	1.81	116	4.12	225	3.32	200	20.13	1,106	7.00	750	8.00	850
moyenne ....	2.21	85	3.58	163	3.19	164	2.48	125	2.19	113	2.58	168	16.13	819	7.59	760	7.33	1,015
B.																		
♂ 50 a. pn. chr. ....	0.16	30	1.21	160	0.66	80	1.33	120	0.91	110	0.97	110	5.24	610				
♂ 56 a. arthr. chr. ...	2.20	180	2.91	270	2.12	110	2.76	70	2.38	50	2.19	60	14.56	740				
♂ 44 a. tbc. pulm. ...	2.14	105	1.31	118	4.41	190	1.22	95	0.87	105	1.58	80	11.53	693				
♂ 67 a. bronchite. ...	1.25	150	1.46	310	0.69	105	1.23	160	1.04	125	1.02	97	6.69	947	6.48	900	22.40	1,400
♀ 65 a. leuc. lymph.	0.37	20	1.57	31	2.99	60	2.30	32	3.73	135	1.41	47	14.57	325	9.31	700	4.65	500
♂ 72 a. ulc. gastr. ...	0.91	30	2.24	30	3.40	38	4.72	93	1.76	60	0.00	000	13.03	251	12.96	900	2.58	430
♂ 44 a. tbc. pulm. ?	1.20	115	2.16	100	2.96	135	2.50	160	2.05	160	1.97	145	12.84	815	12.87	1,550	12.24	1,700
♂ 61 a. ca. pulm. ...	0.00	000	1.40	126	1.09	104	0.70	70	1.98	300	1.83	254	7.00	854	6.60	1,000	4.92	820
moyenne ....	1.03	79	1.78	143	2.29	103	2.09	100	1.84	130	1.37	99	10.68	654	9.64	1,010	9.36	970

Table 2.  
*Hépatites aiguës.*

A. Sujets jeunes; variation de la quininurie et de la diurèse beaucoup moins marquée que chez les sujets jeunes sans lésion hépatique. Valeurs élevées exceptionnelles.  
B. Sujets plus âgés; la même image que dans 2 A.

sex, âge, diagn.	6-8 h.		8-10 h.		10-12 h.		12-14 h.		14-16 h.		16-18 h.		6-18 h.		18-18 h.		18-18 h.	
	quinine	diurèse	quinine	diurèse	quinine	diurèse	quinine	diurèse	quinine	diurèse	quinine	diurèse	quinine	diurèse	quinine	diurèse	quinine	diurèse
A.																		
♀ 38 a.																		
i. inf. ....	2.02	230	2.63	172	2.65	295	1.60	110	2.83	95	1.21	85	12.94	987				
♀ 39 a.																		
i. cat. ....	0.50	50	0.90	74	0.90	70	1.38	78	2.00	115	1.31	94	6.99	481			8.80	1,060
♂ 18 a.																		
i. inf. Lu ...	0.84	150	4.03	395	1.65	78	1.68	95	1.13	75	1.77	130	11.10	923	17.40	1,850	10.65	1,950
♂ 23 a.																		
i. inf. ....	0.40	65	0.75	75	0.81	77	0.70	60	0.95	74	0.38	70	3.99	421	5.40	750	8.30	1,000
♂ 29 a.																		
i. cat. ....	0.95	80	1.18	125	1.17	133	1.03	110	1.31	102	1.48	141	7.12	691	7.81	640	5.70	950
♂ 29 a.																		
i. inf. ....	1.01	40	2.04	56	2.54	50	4.57	103	2.25	97	1.86	84	14.27	430	13.80	920	5.40	900
♀ 28 a.																		
i. inf. ....													12.66	630	10.51	730	6.50	650
moyenne ....	0.95	102	1.92	149	1.62	117	1.83	93	1.75	93	1.33	101	9.87	652	10.98	978	7.56	1,085
B.																		
♀ 49 a.																		
i. inf. ....	2.55	170	3.38	130	2.55	125	1.70	78	2.74	100	2.00	105	14.92	708				
♂ 48 a.																		
i. inf. ....	0.95	70	1.92	138	0.82	90	1.55	160	0.64	120	3.31	290	9.19	868				
♀ 46 a.																		
i. inf. ....	1.38	110	1.86	70	2.29	90	1.10	95	3.37	216	2.06	110	12.06	691	17.01	700	17.92	1,400
♀ 54 a.																		
i. inf. ....	2.70	270	1.41	150	2.62	305	2.68	255	1.69	135	1.08	93	12.18	1,208	9.03	1,050	7.20	1,200
♀ 48 a.																		
i. inf. ....	0.84	40	1.24	109	1.11	100	1.02	68	1.98	200	1.46	105	7.65	632	6.10	650	7.88	730
♀ 45 a.																		
i. inf. ....	0.78	60	0.91	60	1.14	48	2.98	125	1.40	140	1.42	76	8.62	509	9.31	700	6.00	600
♀ 42 a.																		
i. inf. ....													9.03	860	9.33	1,060	10.88	980
♂ 42 a.																		
i. inf. ....													5.36	510	5.56	670		
♂ 52 a.																		
i. inf. ....													10.45	670	20.16	1,400		
moyenne ....	1.53	120	1.79	109	1.75	126	1.84	130	1.97	152	1.89	130	9.94	740	10.93	890	9.98	982

Table 3.

*Cirrhoses hépatiques.*

Variation de la quininurie. Valeurs élevées inexistantes.

sex, âge, diagn.	6-8 h.		8-10 h.		10-12 h.		12-14 h.		14-16 h.		16-18 h.		6-18 h.		18-18 h.		18-18 h.	
	quinine	diurèse	quinine	diurèse	quinine	diurèse	quinine	diurèse	quinine	diurèse	quinine	diurèse	quinine	diurèse	quinine	diurèse	quinine	diurèse
♀ 57 a. c. anascit. . .	0.89	120	0.83	120	3.00	200	3.39	155	3.42	190	3.10	150	14.63	935				
♂ 55 a. c. asc. . . . .	0.85	40	1.55	38	1.22	38	0.76	26	1.16	30	1.08	36	6.62	208				
♂ 72 a. c. ict. . . . .	1.79	85	2.60	200	2.07	170	1.40	98	3.72	280	1.30	102	12.88	935				
♂ 62 a. c. asc. . . . .	1.71	60	0.71	30	0.45	48	0.00	00	0.35	66	0.68	72	3.90	276				
♂ 62 a. c. ict. . . . .	0.98	98	1.39	100	2.32	146	1.08	75	1.12	95	0.38	80	7.27	594				
♂ 56 a. c. asc. . . . .	1.17	94	1.40	65	1.54	62	0.96	60	1.01	32	2.01	56	8.45	369				
♂ 52 a. c. + diab. . .	1.16	60	3.09	215	2.69	210	2.40	240	1.01	90	1.39	125	12.07	940	13.86	1,100		
♂ 62 a. c. asc. . . . .	0.67	58	0.87	94	1.20	80	0.95	82	0.72	54	1.33	120	5.74	488	18.30	1,500	14.00	650
♂ 44 a. c. ict. . . . .	0.87	78	2.10	140	1.50	98	1.94	180	1.18	112	1.17	96	8.76	704	14.85	750	29.00	1,250
♂ 55 a. c. + diab. . .	0.49	65	0.58	75	0.90	108	1.01	122	1.00	151	0.91	145	4.89	666	9.90	1,500	6.50	755
♂ 56 a. c. anascit. . .													10.50	500	9.00	680	9.44	1,025
♀ 46 a. c. ict. . . . .													7.32	470	20.52	950	7.05	750
♂ 57 a. c. asc. . . . .													12.40	310	11.95	480	8.18	250
moyenne . . .	1.12	76	1.51	108	1.69	116	1.39	104	1.48	110	1.34	98	8.88	569	14.05	994	12.36	780

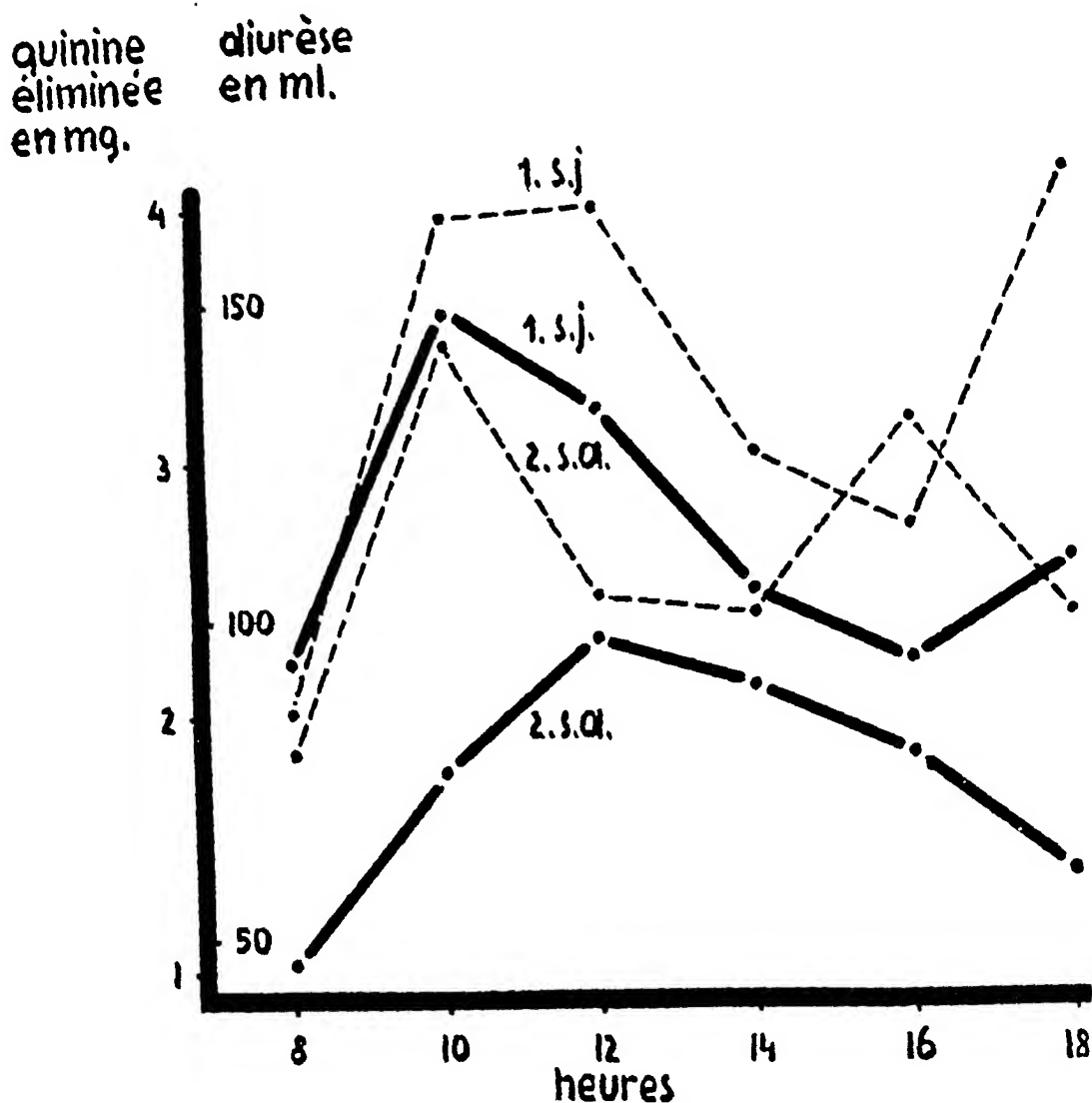


Fig. 1. Courbe moyenne de la quininurie et de la diurèse de 10 sujets jeunes (s. j.) — âge moyen: 24 ans et de 8 sujets plus âgés (s. a.) — âge moyen: 56 a. sans lésion hépatique.

Abscisse: heures où les malades urinent; ordonnée: quininurie et diurèse. Ligne pleine: quininurie; ligne hachurée: diurèse.

Le maximum d'élimination pendant les 6 premières heures chez les sujets jeunes est net. La diurèse est approximativement parallèle à la quininurie. Chez les âgés la courbe de quininurie est beaucoup plus basse, avec le maximum poussé vers la droite. La quininurie n'est pas toujours parallèle à la diurèse.

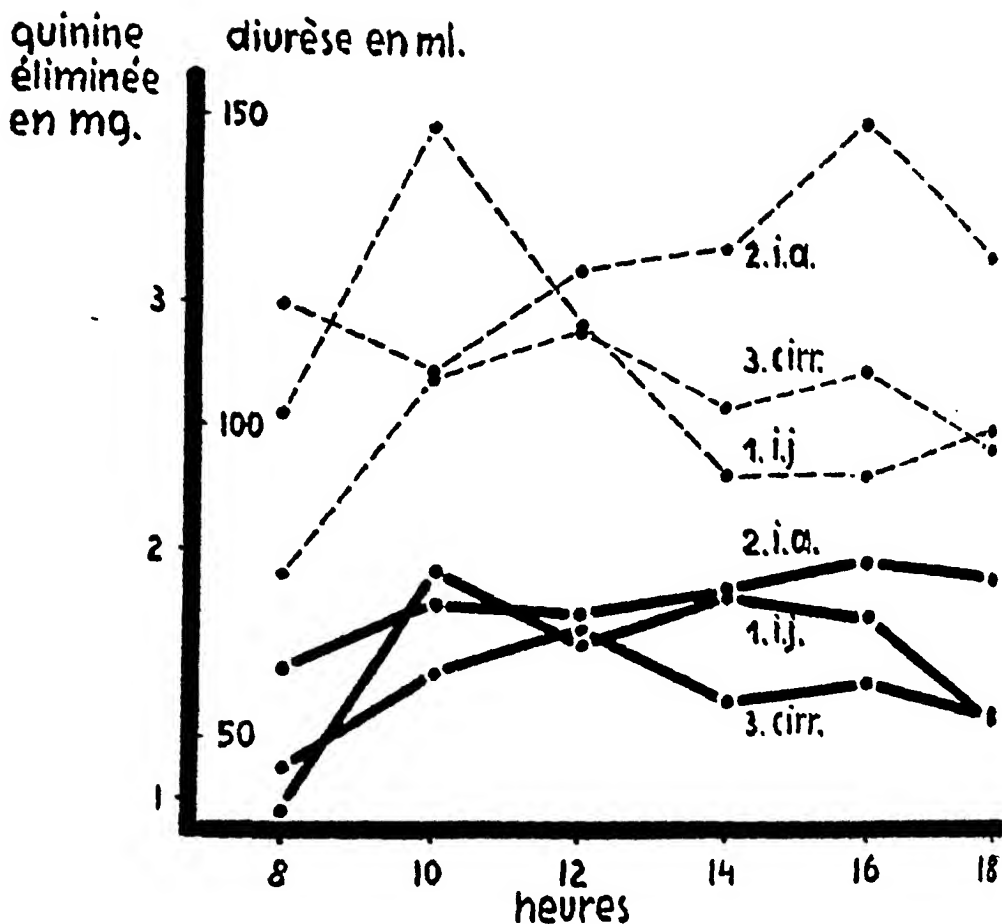


Fig. 2. Courbe moyenne de la quininurie et de la diurèse chez 1) 6 sujets jeunes avec ictère catarrhal ou infectieux (i. j.) — âge moyen: 29 ans; 2) 6 sujets plus âgés avec les mêmes maladies (i. a.) — â. m.: 48 a.; 3) 10 cirrhotiques (cirr.) — â. m.: 58 a.

A noter l'élimination basse, retardée et prolongée. Chez les premiers il y a un léger maximum à la 4-ième heure. La diurèse est aussi retardée et prolongée sauf chez les premiers où il y a un maximum à la 4-ième heure.

## quin. diurèse

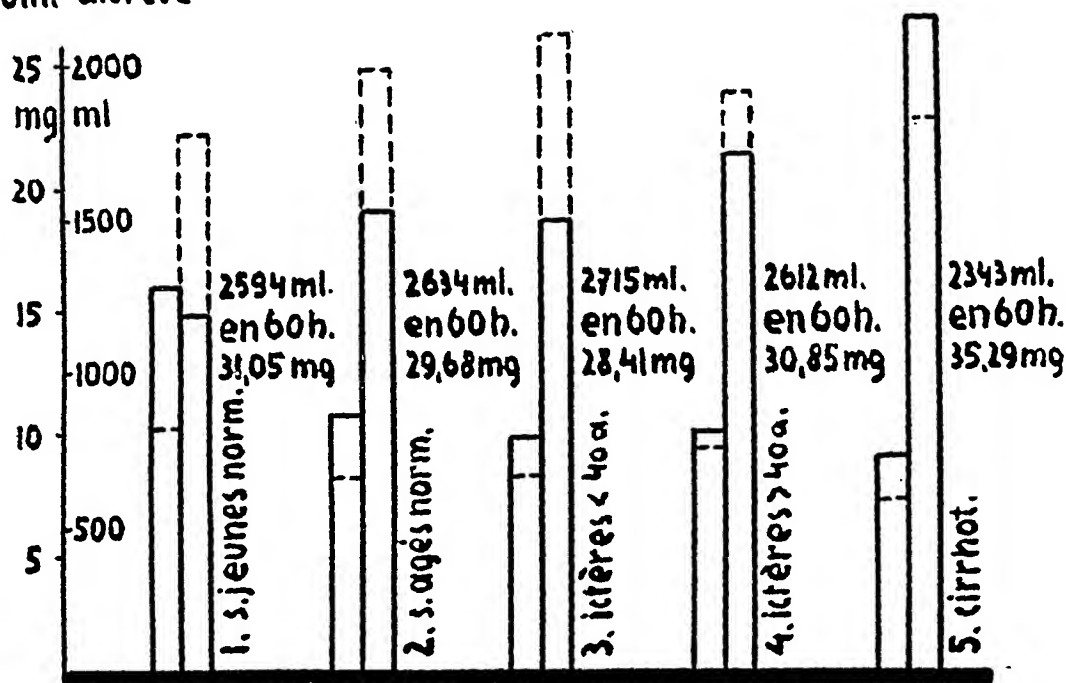


Fig. 3. Elimination de la quinine et diurèse pendant 60 heures. 1) moyenne de 6 cas; 2) m. de 5 cas; 3) m. de 5 à 6 cas; 4) m. de 5 à 7 cas; 5) m. de 6 à 7 cas.

Première colonne: quantité de la q. éliminée dans les 12 premières heures; deuxième colonne: q. éliminée dans les 48 h. suivantes; colonne hachurée: diurèse.

Les sujets jeunes éliminent le maximum de q. dans les 12 premières heures, tandis que chez les autres l'élimination est retardée. La quantité de la q. éliminée en 60 h. est presque identique dans tous les cas sauf chez les cirrhotiques où elle est légèrement supérieure. De même la diurèse totale en 60 heures est approximativement égale partout sauf chez les cirrhotiques où elle est légèrement inférieure.

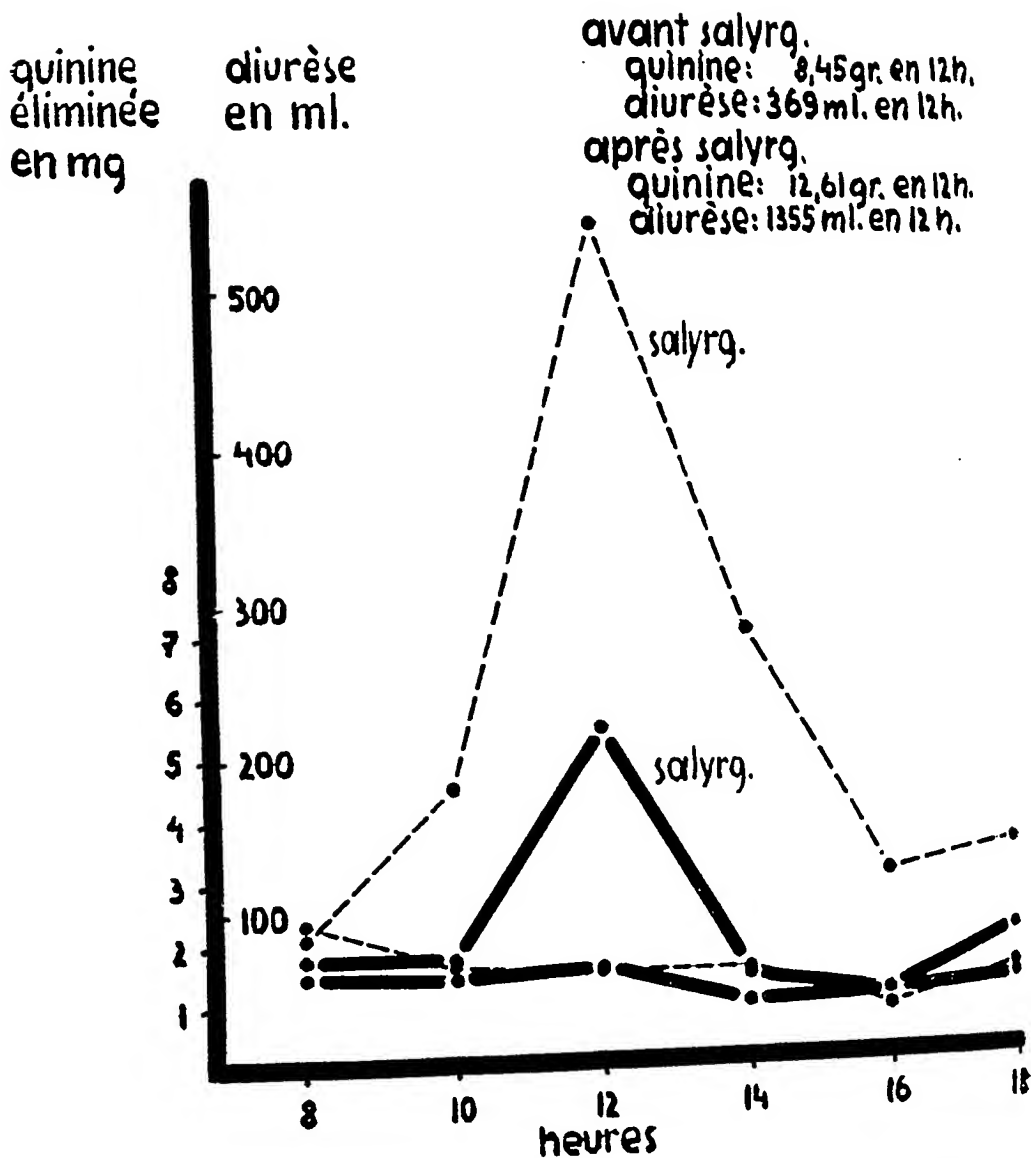


Fig. 4. Diurèse et quininurie provoquée chez un cirrhotique par injection intra-veineuse de 1.5 ml de Salyrgan.

La quininurie augmente après le diurétique; mais elle n'est pas proportionnelle à la diurèse.

*Acta Medica Scandinavica.* Vol. CXXXVI, fasc. II, 1949.

From the Institute of Medical Pathology and Clinical Methodology  
University of Turin (Italy).  
(Director: Prof. P. Sisto).

## Variations of the Mean Diameter in the Ripening of the Erythrocyte.

By

W. PAOLINO.

(Submitted for publication March 8, 1949.)

---

The law by which, increasing in age cells decrease in size, proves true also for the erythrocyte, at least as far as regards the mean globular diameter.

Contrasting results were found by comparing the mean diameter of the erythrocytes obtained from the marrow with the one of the peripheral blood. Starting from the knowledge that the reticulocyte represents an early evolutive stage of the erythrocyte, subsequent studies showed that the former has a larger diameter than the mature erythrocyte.

Nobody, as far as I know, seems to have studied the diametrical changes of the reticulocyte in the various phases of its ripening. This research has seemed to me interesting not only in itself, but also for a more intimate knowledge of some physiopathological problems of the erythrocyte.

These problems refer to the question of the megalonormoblastic transformation of the marrow in pernicious anemia under hepatotherapy; to the alterations of the mean erythrocytic diameter in cases of a sudden erythropoietic revival; to the modified diameter in the course of congenital hemolytic anemia; to the differences of diameters that have been stated between the erythrocytes of the marrow and those of the peripheral blood.

As it has been sufficiently demonstrated that the reticulocytes offers characteristic modifications in the picture of the reticular substance during its ripening, I believe an investigation in this line now possible. As to the criterion of differentiation I followed Heilmeyer's scheme, in which 0 indicates the orthochromatic erythroblast, and I—II—III and IV the different stages of the reticulocyte's ripening. This scheme counts both for the normal as for the greater of the pathological erythropoiesis.



In my preceeding investigations, published in 1945, to the purpose of studying reticulocytosis as an index of erythropoiesis, I verified that the reticular substance is constantly present in all orthochromatic human erythroblasts. Results proved that in leukemias, in most anemias (congenital and acquired hyperhemolysis, in hemorrhagia, in anemia primary or secondary to neoplasms or infective diseases), in Werlhof's and in Hodgkin's disease, the orthochromatic erythroblast always possesses the reticular substance and the maturation develops as in normal cases. On the contrary, the lack of the reticular substance is noted in the orthochromatic erythroblast in hepatic cirrhosis and in primary polycythemia. In the pernicious anemia this phenomenon is constant and of a remarkable intensity. In my researches (10 cases) 22 % to 65 % of the orthochromatic erythroblasts were lacking the reticular substance. Moreover, the same substance was extremely scarce in a high percentage of erythroblasts (from 10 to 24 %), so as it could be presumed that it would disappear before the loss of the nucleus.

This seemed to me sufficient to explain the findings in the pernicious anemia of a reticulocytosis remarkably inferior to the hemolysis, as could be calculated by the bilinogen output. Indeed, in these cases, calculating, with Heilmeyer and Westhausen, the erythrocytic balance by starting from the absolute values of the peripheral reticulocytosis (obtained by the determination of the blood volume), of the hemoglobin and of the bilinogen output, I found a daily deficit of erythrocytes in keeping with the anemizing course, when I corrected the reticulocytic values by adding the percentage of erythroblasts lacking the reticular substance.

With the exception of the pernicious anemia in relapse and in minor degree, the primary polycythemia and hepatic cirrhosis, I found that in all the other hemopathies, and also in different functional states of erythropoiesis, the maturation of the reticular substance proceeds as in normal cases and it is this constancy that allows subsequent investigations.

### Technique of My Researches.

The determinations of the diameter were made on dry smears of blood vitally stained with brilliant-cresyl-blau and after-stained with May-Grünwald's Giemsa solutions. The staining with brilliant-cresyl-blau was effected with the technique already used in my preceeding investigations. Some grains of the staining were put directly on the skin where the blood was issuing and immediately dissolved in the first drops of blood, then stirred and smeared. For the medullary blood, as soon as it was extracted, drops of it were stirred with grains of staining on glass slides and then smeared. Many smears were prepared for every case and those most evenly stained and smeared were chosen for determinations.

Surveys were made on two slides, mean diameters were taken from the measurements of 250 elements of each class of reticulocytes, and to these my data refer. In some cases, especially in those having few reticulocytes and where it was for control purposes, I extracted the diameters of the reticulocytes from the measurements of 500 elements, and those of the erythrocytes from 250 elements. The optical system characteristics were as follows: length of tube 160 mm., Huygens

ocular micrometer 5.8, achromatic objective lens with homogeneous immersion 1/12"; every division of the ocular corresponded to 1.66 micra; the difference between the singly calculated groups is of 0.83 micra.

### Results and Considerations.

My results are founded on 108 reticulo-erythrocytometric pictures, practised in 32 cases contemporaneously on medullary and peripheral blood; in 15 cases only on medullary blood; the remaining 29 refer to researches on peripheral blood only, made on patients who had previously been more completely controlled, or on other patients on whom it had been impossible to practise the medullary biopsy.

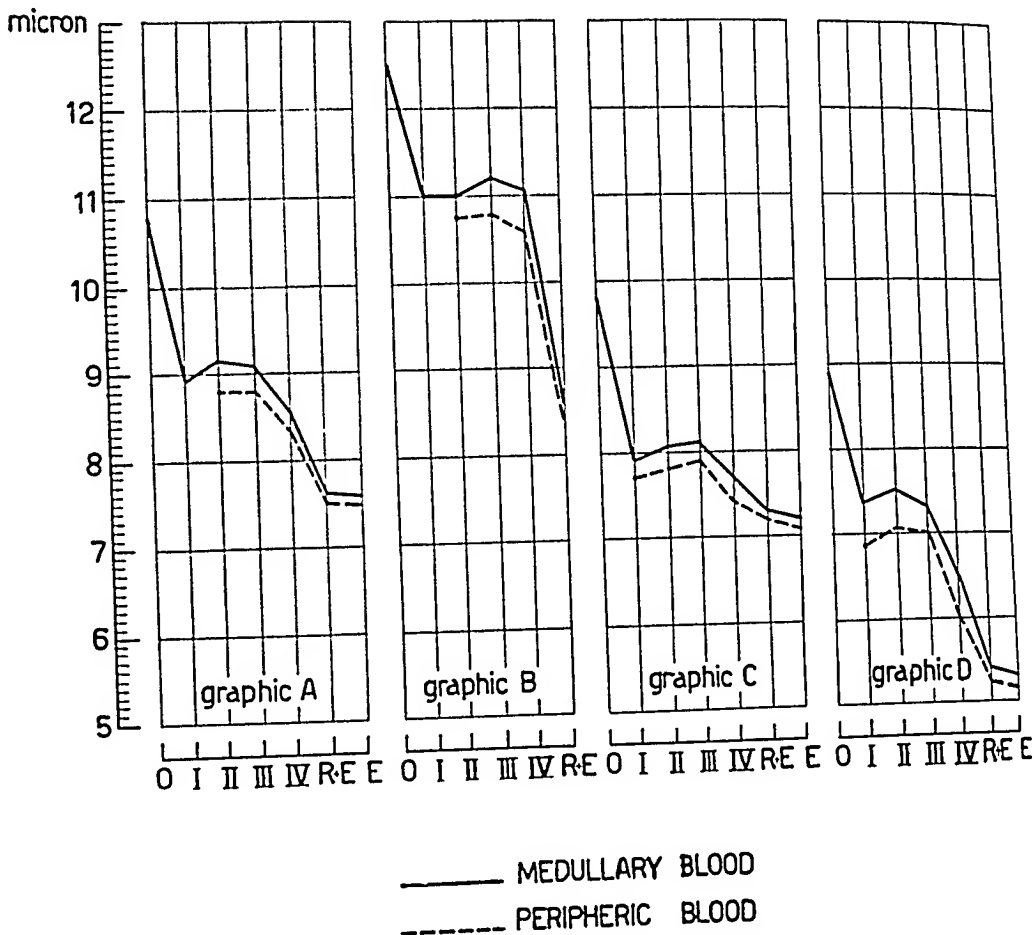
The cases are 57; of these, 6 are young and healthy, 9 are convalescent of infectious diseases with a normal erythropoesis; in these a contemporary determination of the medullary and peripheral blood has been made; 10 cases are of pernicious anemia, of which 4 with medullary controls repeated during the hepatotherapy; 9 cases are of leukemic myelosis and lymphadenosis; 3 are polycythemic, 2 primary and 1 secondary to cardiopathy; 4 cases are of congenital hemolytic anemia; the rest include hypochronic anemias (primary or secondary to hemorrhages or to neoplasms), Werlhof's and Hodgkin's diseases, hepatic cirrhosis and various hepatopathies, etc.

The greater part of the determinations I published in 1946; the subsequent researches, here included, did not alter my conclusions in the least.

I can sum up my observations in 4 types of curves, based on the mean diameters of the various classes studied.

In normal cases, notwithstanding the variability of the biological phenomena and the variations due to unavoidable errors, we can remark a sufficiently constant modality and relationship in the variations of the diameters between the single classes. The commonest form is the one described in curve A. The diameter decreases remarkably passing from the orthochromatic erythroblast to the reticulocyte I; subsequently there is a slight increase with its maximum in class II or III; another decrease follows, so that the IV is generally smaller than the I; after this, the diameter falls further down to the erythrocytes lacking the reticular substance. The decrease of the diameter between the phase 0 and I varies from 0.7 micron to 2.4; in most of the cases over 1.5 micra. Keeping count of the increase corresponding to the intermediate phases, the variations of the diameters of the reticulocytic classes are nearly always included in 1 micron. The mean values of the decline of the diameter in the passage from the IV class of the reticulocytes to the mature erythrocytes are included between 1 micron in the 56 %; between 1 micron and 1.5 in the 38 % and between 1.5 and 1.8 in the 6 %.

The remarkable decline of the diameter observed after the erythroblast points to a sudden loss of the nucleus (by expulsion?). Probably the reticulocytic phase I is brief, after which the cell diameter increases; this increase is probably due to cell flattening. This is not yet proved, but many arguments are in its favour, such as the greater reticulocytic resistance to hypotonic solutions, the slower sedimentation of the reticulocytes, an «ilocyte» look according to Fåhræus.



I have searched for an eventual characteristic alteration of the curve observed in normal subjects as consequence of a variation of the balance between erythropoiesis and erythrodestruction. I found that these variations have very little influence on the picture, which is always in the normal limits. On the other hand, in pathological cases, I observed characteristic pictures.

I once believed that in *pernicious anemia* in relapse no investigation was possible, owing to the alterations in the ripening of the reticular substance previously observed and described. Indeed in these cases, the oscillations of the mean values between the diameters of the single reticulocytic classes are disorderly. However a constant data is the remarkable difference between the reticulocytic classes diameter and that of the erythrocytes lacking the reticular substance. In normal cases I found that only in a 6 % the difference between the cell diameter reached a maximum from 1.5 to 1.8 micra. On 10 cases of pernicious anemias only 2 showed a mean value that went from 1.5 to 2 micra, while in the other 8 cases the difference was always more than 2 micra and often much more (see in graphic B a case with a mild difference).



bulk, but also between elements belonging to the same reticulocytic classes (see graphics). The conclusion based on this fact is that the differences of the diameter between the erythrocytes of the two districts do not indicate differences of age, but modifications of the erythrocytes due to the different conditions of the environment and independent of whatever be their ripening stage.

Lastly, I wish to refer the data obtained from the measurements of the mean diameter of the basophilic punctuated erythrocytes. It is now past discussion the generative or degenerative nature of these grains and their nuclear or cytoplasmatic derivation. However as no other studies have been made, as far as I know, on the diameter values of these erythrocytes, I believe it may be interesting to refer my observations. I have been able to study 5 cases of anemia with a high percentage of basophilic punctuated erythrocytes, *i. e.*: 1 case of hemocytoblastic myelosis; 2 cases of pernicious anemia; 1 case of anemia secondary to gastric neoplasm, 1 case of lead poisoning. The mean diameters are the following:

	I	II	III	IV	V
M. Diameters of erythrocytes .....	7.22	8.46	8.81	6.84	7.09 micron
»       »       of basoph. punct erythro-					
cytes .....	8.23	9.25	9.52	7.79	7.97 »

The difference between the two mean diameters is about 1 micron. Therefore the basophilic punctuated erythrocytes are as large as the erythrocytes at the reticulocytic stage and can thus be considered as young cells.

### Summary.

The ripening of the reticular substance of the erythrocytes evolves, in most illnesses, as in normal subjects.

An exception to this rule is the pernicious anemia in relapse, in which the reticular substance is, in a high percentage, already lacking the orthochromatic erythroblasts, or else is so scarce that it could be presumed it would disappear before the loss of the nucleus. The early disappearance of the reticular substance explains the reason why, in this disease, the peripheral reticulocytosis is generally greatly inferior to the erythrogenesis, as can be calculated by the bilinogen output.

A slight precocious ripening of the reticular substance, if compared with the nucleus ripening, can be remarked also in the polycythemia and in the hepatic cirrhosis, though in a minor degree.

In *normal subjects* the measurements of the diameter of the orthochromatic erythroblasts, of the single classes of reticulocytes and of the ripe erythrocytes show that the mean diameter decreases from 0.7 micron to 2.4 (from 1.5 to 2.4 in the majority of cases) in the passage from the orthochromatic erythroblast to the reticulocyte of the I class. This remarkable decline points to a sudden loss of the nucleus (by expulsion?). The diameter increases passing from the I to II—III class, but subsequently decreases in the passage to the IV class, which shows always a mean diameter inferior to the I class. These oscillations are usually

limited to 1 micron. The increase of the cell diameter in the II and III class can only be explained by cell flattening. There is a further decline from the IV class to the mature erythrocytes and this decline, in the reported cases, was never superior to 1 micron in the 56 %, was of 1 to 1.5 micra in the 38 % and of 1.5 to 1.8 in the 6 %.

In the *pernicious anemia* the relationship between the diameters of the single reticulocytic classes is disorderly, owing to the alterations in the ripening, described before. A constant data, in these cases, is a remarkable decrease of the diameter in the passage from the IV class to the mature erythrocyte (of 10 cases only 2 had a difference of 1.5 micra to 2; in the other 8 cases the difference always exceeded 2 micra, and often much more). This great diversity suggests that in *pernicious anemia* the hyperhemolysis is at the expense of the giant cells of the more immature classes.

In cases of *continual hyperhemolysis* with a contemporaneous marked production there is the smallest difference between the various diameters.

In *hemolytic jaundice*, apart from the decrease of the diameter, the relationship of the single classes is the same as in normal cases; this suggests the idea that the hyperhemolysis charges on a certain set of erythrocytes and not on a certain stage of their ripening evolution.

The *regenerative erythromacrocytosis*, parallel to an increased reticulocytosis, is due to a bigger number of young cells and not to the production of a larger erythrocytic generation.

In the *pernicious anemia*, in the first stages of recovery, the study of the metrical curves of the I reticulocytic class does not reveal any sudden appearance of smaller cells, thus suggesting the hypothesis of a normocytic transformation of megaloblasts.

The diameter difference between the erythrocytes of the *medullary blood* and those of the *peripheral blood* are not bound to the age of the cell, but to changes of environment, as the same difference is remarked in the single stages of the reticulocytic maturative evolution.

The *basophilic punctuated erythrocytes* have a diameter larger than the respective ripe erythrocytes; the difference is the same as the one between ripe erythrocytes and reticulocytes.

#### Literature.

Heilmeyer, L. and R. Westhauser: Z. klin. Med. 1932—121—361. — Paolino, W.: Min. Med. 1945—II—181; II—216; 1946—I—327.

---

From the Medical Department of the Hålsingborg Hospital, Sweden.  
(Chief: Prof. Th. Stenström, M. D.)

## Acute Myeloblastic Leukemia and Insufficiency of the Bone Marrow.

By

SVEN JOHNSON.<sup>1</sup>

(Submitted for publication April 6, 1949.)

Acute myeloblastic leukemia, and especially its variants and etiology, has been discussed recently. (It is not the purpose of this paper to discuss whether acute lymphatic leukemia exists. The cells are often too primitive to permit any conclusion. Naegeli and Schulten denied the existence of acute lymphatic leukemia, but Arneth does not agree with them). The discussion has centred around the relationship of the acute leukemias to the chronic myeloid leukemias and also to the various conditions of insufficiency of the bone marrow *i. e.* agranulocytosis, aplastic anemia and panmyelophthisis.

Naegeli believed that the acute leukemias had no connection with the various types of bone marrow insufficiency. Acute leukemia is a true leukemia and thus necessarily a fatal systemic disease. According to Naegeli the leukemias are caused by a disturbance of unknown type which has nothing to do with tumours or infections.

Apitz, Moeschlin, Rohr, Schulten, and others share Naegeli's view, *e. g.* that the acute leukemias have no etiological connection with bone marrow insufficiency. They consider that acute and chronic leukemia have much in common, but unlike Naegeli believe that the two types of leukemia are of tumour-like origin.

In recent years many authors have disagreed with this theory. Ferrata, Henning, Hoff, Waldenström, Sternberg, Voit and Landes, and others consider that the acute and chronic leukemias are essentially different in their pathogenesis. They regard the acute leukemias as closely related to the various insufficiency states of the bone marrow (agranulocytosis, aplastic anemia and panmyelophthisis) and assume, therefore, that acute leukemia is a reaction and not a tumour-like disease.

Stodtmeister and Büchmann, and others attempted a mixture of the two theories. They think that the reactive hyperplastic bone marrow found in agranulocytosis,

<sup>1</sup> Allmänna sjukhuset, Malmö (Sweden).

for instance, may become neoplastic when exposed to certain irritative or deficiency factors. The myelogenous insufficiency would thus sometimes correspond to a pre-cancerous initial stage of acute leukemia which is supposed to be of tumour-like origin.

If acute leukemia is regarded as a real leukemic systemic disease it follows that acute leukemia is a fatal and progressive disease. Some aspects of the disease, however, are difficult to reconcile with this theory. These diseases are often impossible to distinguish from true leukemia, either clinically or by studies of the bone marrow. They show, however, prolonged remissions with a normal blood count and normal bone marrow.

Those who believe that the acute leukemias are actually leukemic explain the cases which recover or have prolonged remissions as being leukemoid reactions and not true leukemias (Rohr, Schulten and others). They do, however, admit that in a few rare cases an acute leukemia cannot be distinguished from a leukemoid reaction even at autopsy (Rohr, Schulten). If the patient dies the diagnosis is therefore acute leukemia, but if he survives the disease is said to have been a leukemoid reaction. According to Rohr leukemia causes central damage to the bone marrow, while agranulocytosis begins peripherally in the blood. Acute leukemia may produce an accompanying agranulocytosis, and agranulocytosis may cause a leukemoid reaction. In order to explain the many myeloblasts sometimes seen in the bone marrow in agranulocytosis he assumes that the myeloblastic proliferation is a reaction while in acute leukemia the proliferation has a neoplastic character. The fact that myeloblasts are also found in the liver and the spleen in conditions which he regards as leukemoid reactions is explained by metaplasia, while the same changes in acute leukemia are interpreted as metastases.

The authors who believe that the pathogenesis of acute leukemia is reactive and differs from chronic leukemia, base their opinion mainly on the cases of acute leukemia which had complete remissions and the few cases which recovered completely.

Gloor (1930) described a case with a typical clinical picture of acute leukemia. The blood count showed at first 15,600 leucocytes with 91 % small atypical myeloblasts. The leucocytes increased to more than 100,000, still with more than 90 % myeloblasts. The leucocytes later fell rapidly to 955. Myeloblasts disappeared entirely and granulocytes reappeared. After 2½ years the blood count was quite normal. No bone marrow biopsy was made.

Roth (1943) described a case with a clinically typical leukemic picture. Bone marrow biopsy showed at first 85 % paramyeloblasts, but 2½ months later, when the patient had recovered and had a normal blood count, bone marrow biopsy was quite normal. During recovery the leucocytes increased from very low values to more than 100,000 and myelocytes appeared. The patient was observed only for 3 months.

Complete remissions in acute leukemia have been described by Jackson (remission lasted 3½ months), Evensen and Schartum-Hansen (3—5 months in 3 cases), Hoff (6 months), and by Petrén and Odin (18 months).

Naegeli and others explain these complete remissions in acute leukemia by saying



that the first attack is a leukemoid reaction while the second attack is regarded as real acute leukemia.

The advocates of the reactive theory point out that a close relationship exists between the various insufficiency states of the bone marrow (agranulocytosis, aplastic anemia and panmyelophthisis) and the acute leukemias. They maintain that agranulocytosis, particularly during recovery may sometimes present a picture which is indistinguishable from acute leukemia. Blood count with up to 100,000 leucocytes and many atypical myeloblasts can be observed, the hiatus leukemicus may be present, and the spleen and liver may be enlarged. Later the hiatus is overcome by the appearance of intermediate forms and, finally, the blood count becomes completely normal. Such fully healed agranulocytotic conditions with myeloblastic reaction have been described by Schilling, Kissling and others as leukemoid reactions and they were distinguished from the acute leukemias.

It is possible, however, that in connection with agranulocytosis an acute leukemic picture may develop in which no maturation of myeloblasts occurs, but the acute leukemic picture persists and leads to death. The leukemic picture may appear either in direct connection with agranulocytosis or with an intermediate stage of remission with clinically normal health. Such agranulocytotic conditions which are generally accompanied by a decrease of red cells and platelets, *i. e.* panmyelophthisis, have been reported after complete remission to have changed into acute leukemia and at autopsy the findings were typical of the disease (Meuwesen, Palmén, Szonell, Voit and Landes, and others). These cases are characterized by:

1. a comparatively short duration — 1 week to 6 months for the entire course of illness.
2. a particularly acute course of the disease during the leukemic stage resulting in death after 1—2 months.

The blood count shows at first:

1. leukopenia with granulocytopenia,
2. anemia,
3. thrombocytopenia.

Later the blood count shows:

1. the typical blood picture of acute myeloblastic leukemia:
  - a. increased number of leucocytes,
  - b. 80—100 % myeloblasts,
  - c. hiatus leukemicus.
2. anemia.
3. thrombocytopenia.

Because of such observations several authors, such as Hoff, Meuwesen, and Voit and Landes, have put forward the theory that the various forms of bone marrow insufficiency (agranulocytosis, aplastic anemia, panmyelophthisis) and acute leukemia are, not two different diseases, but merely different forms or stages of the same disease. The characteristic features of this morbid state are its course and the remissions and recurrences. The same patient may suffer from combinations of various types of insufficiency of the bone marrow, for instance, agranulocytosis

—acute leukemia—recovery; agranulocytosis—acute leukemia leading to death; agranulocytosis—remission—acute leukemia; aplastic anemia—acute leukemia; panmyelophthisis—acute leukemia.

Hoff regards the various forms of myeloid insufficiency as alternating phases. In all forms of myeloid insufficiency prolonged remissions, followed by relapses with or without phase alternating or recovery may occur. Prolonged remissions may occur also in acute leukemia; even recovery is possible, although rare.

According to Hoff and others acute leukemia is a frustrated compensatory hyperplasia of the bone marrow. The functioning bone marrow at first produces very primitive cells (myeloblasts). This myeloblastic reaction should be interpreted as a tendency to recovery. Even after complete interruption of maturation (hiatus leukemicus) normal leucocytes can be produced by maturation of myeloblasts via intermediate stages. In this way the blood count becomes completely normal. Such a phase in the development occurs, for example, in agranulocytosis which may heal with a transitional stage of acute leukemia.

Severe infections, toxic substances, agranulocytosis, panmyelophthisis, and chronic leukemia may provoke compensatory myeloblastic hyperplasia of the bone marrow and acute leukemia may result. In most cases, however, the myeloblasts cannot mature and the patient dies with the symptoms and signs of acute leukemia.

A case of acute leukemia is reported here as a contribution to the discussion of the etiology of acute leukemia. After an acute illness with the typical findings of acute leukemia a remission occurred accompanied by the disappearance of all the paramyeloblasts from the blood and the bone marrow. The only persisting evidence of myeloid insufficiency was granulocytopenia. This remission lasted only about one month and was followed by a new attack of acute leukemia, leading to death after 8 months. The autopsy confirmed the diagnosis of acute leukemia.

### Report of Case.

A man of 32 years has been healthy previously. No blood dyscrasias noticed in the family. 2½ months before admission on December 28th 1946 he complained of pain in the back of the head and of nausea. A few days before admission he fell ill with shivering, fever and headache, but no signs of upper respiratory infection.

He was pale but there were no haemorrhages in the skin. The tonsils were slightly enlarged but only a little inflamed. At the right angle of the jaw there was a small lymph gland which was slightly tender. Otherwise there were no enlarged glands. The liver and spleen were not felt. Radiographs of the lungs were normal. Blood count: Hemoglobin (Autenrieth) 46 %, RBC 2.27 million, WBC 15,600; paramyeloblasts 99 %, neutrophils 1 %; platelets 149,000. Sedimentation rate: 138 mm per hour.

Sternal puncture: Paramyeloblasts 81.2 %, myelocytes 6.6 % (neutrophils 3.2 %, eosinophils 2.6 %, basophils 0.8 %), metamyelocytes 1.4 %, lymphocytes 2.2 %, plasma cells 0.8 %, reticulum cells 0.6 %, proerythroblasts 0.2 %, erythroblasts 1.8 %, damaged cells 5.2 %.

The patient was given frequent blood transfusions (2—3 times per week; usually 450 ml blood each time) and penicillin 200,000 units per day. During the first month the patient's condition remained practically unchanged with a remittent pyrexia. Ulcers appeared on the scrotum and around the anus. In spite of blood transfusions the anemia did not

improve. The leucocytes remained less than 10,000 and sometimes there were only 2,500, but almost all the cells were paramyeloblasts. The sedimentation rate was always more than 100 mm per hour.

During the next fortnight (1 month after the onset of illness) there was a marked improvement in the patient's general condition: appetite increased, temperature became normal, the ulcers healed. The white blood corpuscles were now between 1,000 and 2,000, mature leucocytes began to reappear and the paramyeloblasts decreased in number (only few myelocytes were seen in the peripheral blood). The sedimentation rate fell to about 50 mm. The hemoglobin rose to 80 % and the red cells increased to 4 million.

The patient remained afebrile until the beginning of April. The general condition improved during this time and his weight increased by 10 kg. The blood count showed marked improvement. The hemoglobin remained mostly at 80 % and the red cells were usually about 4 million, the platelets increased to 205,000. The leucocytes varied between 1,000 and 2,000. The paramyeloblasts disappeared completely but only 28 % were neutrophil granulocytes. The sedimentation rate fell gradually to 26 mm. Sternal puncture on March 26th 1947 showed the following count: Myeloblasts 0.6 %, promyelocytes 1.6 %, myelocytes 9 % (neutrophils — 8.2 %, eosinophils 0.6 %, basophils 0.2 %), metamyelocytes 6.2 %, mature granular cells 12 % (neutrophils 5.8 %, unsegmented neutrophils 5.4 %, eosinophils 0.8 %), lymphocytes 38.6 %, plasma cells 0.4 %, reticulum cells 1.4 % larger mononuclear cells 5.2 %, normoblasts 10.8 %, damaged cells 14.2 %.

«The picture of the bone marrow was quite different from that of December 30th 1946. When the unexpected course of the disease is taken into consideration one must doubt the diagnosis of acute leukemia made at the first examination. The histological preparation from that material, however, showed proliferation of an atypical immature cellular kind and agreed well with this diagnosis. It could, therefore, not be expected that the blood formation would return to normal.» The sternal marrow from the second puncture has also been examined by Dr Nordenson who expressed the opinion that a normal though scanty myelopoiesis was present. He did not consider the bone marrow as leukemic.<sup>1</sup>

The patient remained at his home from April 5th to April 8th. On his return there was slight pyrexia and the temperature rose to 40° C. after a few days. The temperature lasted for a month. At the same time the red cells decreased and the leucocytes were around 2,000. The number of mature granulocytes fell while the paramyeloblasts reappeared and increased gradually to about 90 %. The sedimentation rate rose to 117 mm. The number of blood transfusions which had been reduced to 1 per week were increased to about 3 per week and the dose of penicillin was increased to 240,000 units daily.

At the beginning of May the patient was again afebrile, the hemoglobin was about 80 % and the erythrocytes about 4 million. The leucocytes increased slowly during May and June to about 10,000 of which more than 80 % were paramyeloblasts. A sternal puncture made on May 8th showed again 45 % paramyeloblasts. On June 26th the paramyeloblasts in the marrow had increased to 70 %, on July 31st to 78.4 %, and on October 24th to 86.4 %. This last preparation has also been examined by Dr Nordenson who diagnosed acute myeloid leukemia.

Later on the leucocytes increased gradually and reached 113,000 in September, and more than 0 % were paramyeloblasts. Urethane was then given and the leucocytes fell to 19,500. When urethane was discontinued the leucocytes increased once more to 80,000. Another course of urethane reduced the leucocytes to 42,100. The general condition gradually deteriorated with a rising temperature, and the patient died on December 23rd 1947, one year after the onset of the illness. The leucocytes were then 214,000 and almost all were paramyeloblasts. Since July the liver and spleen had been enlarged and towards the end they became so large that they reached 13 and 4 cm respectively below the costal margin. For a study of the course of the illness see the charts 1 and 2.

*Autopsy:* The liver weighed 4,000 g and the spleen 2,200 g. The kidneys were enlarged,

<sup>1</sup> I am grateful to Dr Hellsten and Dr Nordenson for the sternal puncture findings.

and the cortex was grey and wider than normal. Each kidney weighed 225 g. Many hemorrhages were observed in the pericardium and in the pleurae.

*Microscopical Examination:* The bone marrow was homogeneous and most cells were immature myeloid forms. Most cells were blast cells with round nuclei, rich in chromatin. There were, however, also some myelocytes and a few eosinophils. In the liver marked infiltration of immature myeloid cells was seen both in the connective tissue of the portal tracts and between the liver cells. Most of the cells were of the blast type. The Malpighian

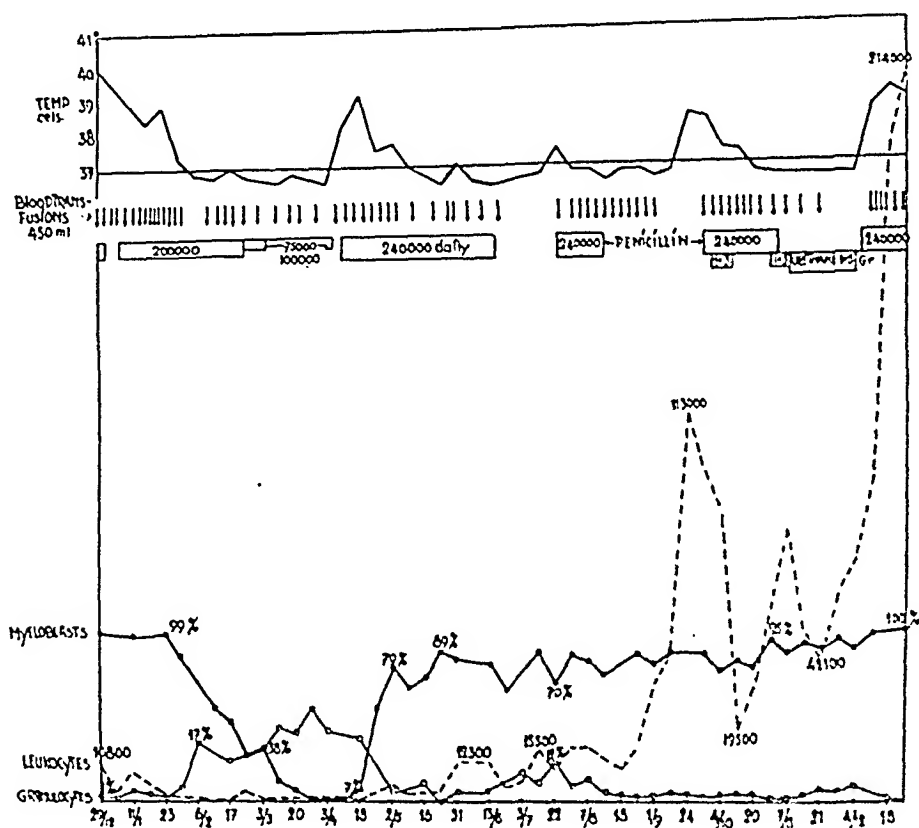


Chart 1. Number of leucocytes, percentage of myeloblasts and granulocytes, temperature (approximately one reading per week) and amount of blood transfusions, penicillin and urethane.

bodies were not distinguishable in the spleen and there was massive diffuse infiltration with myeloid cells of the same type as in the liver. In the kidneys, and especially in the cortex, marked leukemic infiltration was seen.<sup>1</sup>

The course of the disease consisted of 3 phases: acute leukemia—remission with granulocytopenia—acute leukemia.

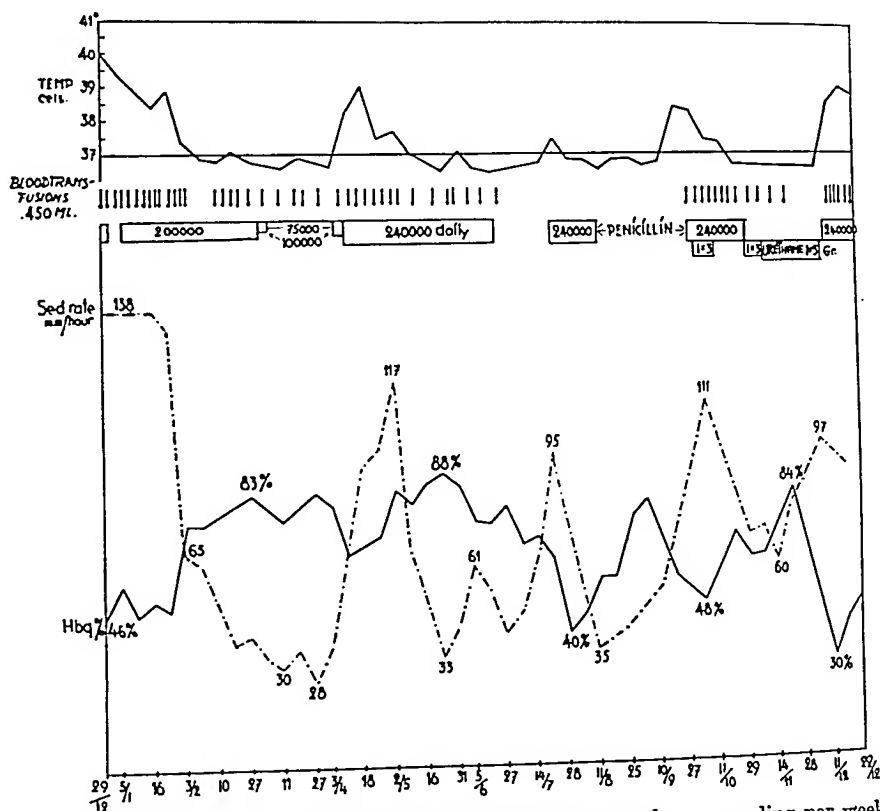
### Comment.

There is no doubt that acute myeloblastic leukemia existed during the third and fatal phase. The autopsy showed the presence of myeloblasts in the bone marrow and in liver, spleen and kidneys. These findings together with the blood count

<sup>1</sup> I am grateful for the microscopical examination of the section kindly made by Dr Linell.

of more than 100,000 leucocytes most of which were paramyeloblasts, without intermediate forms (hiatus leukemicus) settled diagnosis of acute leukemia.

In the initial phase the picture was that of acute leukemia. Fever, a high sedimentation rate, a moderate increase of leucocytes with definite hiatus leukemicus and 99 % myeloblasts are findings which supported this diagnosis. Bone marrow biopsy showed 81.2 % of the same primitive cellular type as in the blood. The cells did not resemble any type normally present in the bone marrow. They resembled



the cells which Naegeli called paramyeloblasts. Some authors maintain that in leukemoid reactions, for instance in agranulocytosis, the myeloblasts are normal in character while those in acute leukemia are pathological. Since paramyeloblasts do not normally occur in the bone marrow this finding supports the diagnosis of acute leukemia also for the initial phase. This fact as well as the similarity between the pathological pictures of the first and third phases, with paramyeloblasts of the same appearance justifies the diagnosis of acute leukemia also for the first phase. To call the first phase agranulocytosis with leukemoid reaction and the third phase acute leukemia, would be incorrect, since no difference could be observed between the two phases either clinically or hematologically. The fact that the patient was much improved during the first phase while the third proved fatal cannot alone justify different diagnoses for the two otherwise identical pathological conditions.



### Summary.

The various theories of the pathogenesis of acute leukemia are reviewed. Two differing ideas dominate the literature:

1. Acute leukemia is a real leukemia and is an irreversible morbid condition with fatal end result.
2. Acute leukemia is of a reactive nature and closely related to the various forms of myeloid insufficiency (agranulocytosis, aplastic anemia, panmyelophthisis).

A case is reported which was followed for 1 year during which frequent examinations of the blood and bone marrow were carried out. The following pathological pictures occurred: acute leukemia—remission with moderate granulocytopenia as the only finding indicating abnormality—acute leukemia with fatal end result.

The possible diagnosis of agranulocytosis with leukemoid reaction for the first phase of the illness is discussed but is considered to be improbable. The course of the illness can only be explained by the theory that acute leukemia is a reactive disorder. The infection accompanying the disease should be combatted by penicillin and frequent blood transfusions in the hope that the myeloblastic bone marrow may mature and function once more.

### References.

- Apitz: *Virchows Arch.*, 299, 1937, 1. — Arneth: *Folia haemat.*, 62, 1939, 145. — Even-  
sen & Schartum-Hansen: *Acta Med. Scand.*, 107, 1941, 227. — Ferrata: *cit. by Hoff.* —  
Gloor: *Münch. Med. Wschr.*, 1930, 1093. — Henning: *Dtsch. Arch. klin. Med.*, 178, 1936,  
538. — Hoff: *Z. klin. Med.*, 140, 1942, 128. — Jackson, *Amer. J. med. Sci.*, 188, 1934, 604.  
— Kissling: *cit. by Hoff.* — Meuwesen: *Klin. Wschr.*, 21, 1942, 273. — Moeschlin & Rohr:  
*Ergebn. inn. Med.*, 57, 1939, 723. — Naegeli: *»Blutkrankheiten und Blutdiagnostik*,  
Berlin, 1931. — Palmén: *Acta paediat.*, 30, 1943, 324. — Petrén & Odín: *cit. by Hoff.* —  
Rohr: *»Das menschliche Knochenmark*, Leipzig, 1940. — Idem: *Schweiz. Med. Wschr.*,  
74, 1944, 215. — Roth: *Schweiz. Med. Wschr.*, 73, 1943, 1202. — Schilling: *»Das Blutbild  
und seine klinische Verwertung*, 1933. — Schulten: *»Lehrbuch der klinischen Haemato-  
logie*, Leipzig, 1939. — Idem: *Verh. dtsch. Ges. inn. Med.*, 1940, 271. — Idem: *»Erkennung  
und Behandlung der Leukämien*, Stuttgart, 1942. — Stodtmeister & Büchmann: *Klin.  
Wschr.*, 1941, I, 329, 419, 475. — Szonell: *Klin. Wschr.*, 1940, I, 1137. — Waldenström:  
*Nord. Med. Tid.*, 1943, 2359. — Voit & Landes: *Klin. Wschr.*, 17, 1938, 885.





the history of medicine have here a treasure-house and a reliable reference work. There is also reason to bear in mind the importance emphasized in several places, and by widely different authors, of instruction in both the international and the national history of medicine, and perhaps also in the purely local as at The Ohio State University. How long will it be considered that the medical teaching in a culture nation like our own is able to dispense with an orientation in these matters, which create for the students the background of what takes place within the medicine of our time and will take place in the future?

*Wolfram Kock, Stockholm.*

---

## Étude des tracés électrocardiographiques de 314 cardiopathies congénitales.<sup>1</sup>

Par

E. DONZELOT, A. M. EMAM ZADE, R. HEIM DE BALSAC et C. METIANU.<sup>2</sup>

(Ce travail est parvenu à la rédaction le 7 Janvier 1949.)

Venant d'étudier très complètement 314 cardiopathies congénitales adressées depuis un an au Centre des Enfants Bleus, l'examen électrocardiographique de ces sujets a spécialement retenu notre attention. L'importance des documents recueillis par nous, nous incite à en présenter les principales données et à essayer d'en dégager quelques conclusions. En raison de la complexité d'un tel sujet, nous éviterons toute interprétation ou toute discussion qui nous entraînerait à reprendre un exposé de l'ensemble des connaissances électrocardiographiques. Nous nous bornerons donc à la présentation des faits.

### Matériel d'étude.

Ce travail porte sur 264 cardiopathies cyanogènes dont 200 tétralogies de Fallot et 50 cardiopathies sans cyanose. Cette disproportion vient du fait que notre Centre, créé pour réaliser des interventions chirurgicales du type Blalock-Taussig, n'a reçu que des malades en partie triés par leurs Médecins-traitants et, surtout, des enfants cyanosés. De ce fait, la fréquence relative de chaque maladie se présente dans notre statistique d'une façon particulière.

L'âge de nos enfants s'échelonne entre 20 mois et 20 ans et surtout de 4 à 15 ans. Nous ne comptons que deux enfants seulement âgés de moins d'un an, douze malades de 21 à 30 ans, un de 31 ans (syndrome de Lutembacher) et, enfin, un de 45 ans (arc aortique à droite et isolé).

Pour établir un diagnostic relativement précis, nous avons effectué les examens cliniques, radiologiques et biologiques les plus complets, chaque malade restant

<sup>1</sup> Travail du Centre des Enfants Bleus de l'Hôpital Broussais (Clinique Cardiologique de la Faculté de Médecine de Paris: Pr. E. Donzelot et collaborateurs: Drs A. Pithon, R. Heim de Balsac, A. M. Emam Zade, J. E. Escalle, M. Durand, C. Metianu. Service de Chirurgie: Pr d'Allaines et Collaborateurs: Drs G. Dubost, A. Toupet, N. du Bouchet, J. le Brigand. Service Central d'Electroradiologie: Drs Foubert et Collaborateur: Dr Antoine. Ont également participé aux travaux du Centre: Drs Dessertenne, S. Collado, Madera & M. Kolosy, Guery & Passelecq).

<sup>2</sup> Depuis la rédaction de ce travail 300 cas ont encore été examinés. Les modifications électrocardiographiques observées dans ces derniers cas concordent dans les grandes lignes avec nos constatations antérieures.

entre nos mains au moins quatre jours. Dans 68 cas où les moyens habituels ne nous paraissaient pas satisfaisants, nous avons pratiqué, en plus, 58 fois une angiocardigraphie. Nous avons eu, en outre, la possibilité de vérifier 16 cas à l'autopsie. Malgré cela, dans 16 cas, la complexité des malformations et des discordances entre les différents éléments séméiologiques nous ont imposé de ne pas conclure. Dans les 298 cas restants, nos diagnostics semblent exacts; mais, nous n'ignorons pas que, dans toutes les cardiopathies congénitales, la vérification anatomique dément le diagnostic posé durant la vie dans une proportion d'au moins 10 %.

### Technique.

Les tracés électrocardiographiques ont été enregistrés, en grande partie, à l'aide de l'appareil à corde à une vitesse de 33 mm/sec., »l'appareil à lampe (50 mm/sec.) et l'appareil à oscillographe cathodique (35 mm/sec.) ayant été utilisés bien plus rarement. Les différentes dérivations n'ont pas été enregistrées simultanément mais successivement.

Aucun malade n'a été soumis à la digitalothérapie avant le prise des tracés.

Des unipolaires augmentées des membres ont été enregistrées dans 96 % des cas, et, des dérivations thoraciques multiples dans 30 % des cas. Les tracés ainsi obtenus confirment les données acquises sur les dérivations périphériques simples.

La boucle vectorielle a été reconstruite dans tous les cas, et, nous plaçant sur le terrain vectographique, nous avons considéré, dans les ondes rapides, la première déflexion comme étant l'onde Q, la deuxième et la troisième comme R et S, qu'elles soient positives ou négatives.

Nous avons enregistré, à l'aide de l'oscillographe cathodique, un certain nombre de boucles vectorielles — boucles électro-négatives — qui feront l'objet d'un autre travail.

Dans tous les tracés, nous avons évalué, d'une part, l'axe moyen de QRS et, d'autre part, l'axe particulier de chacun de ses composants.

### Faits observés.

Nous considérons successivement:

- 1°) l'axe de QRS,
- 2°) les rapports particuliers entre l'axe de R, de S, du segment ST et de l'onde T,
- 3°) l'allongement de la durée de QRS,
- 4°) les modifications de l'onde P,
- 5°) les modifications de l'intervalle P—R,
- 6°) les troubles du rythme.

#### I. L'axe moyen de QRS.

Le tableau I, présenté suivant les différents secteurs du cercle vectoriel et les cardiopathies, indique la position de l'axe de QRS.

Axe moyen de QRS par rapport aux 314 cardiopathies congénitales  
(264 avec cyanose, 50 sans cyanose).

ÉTUDE DES TRACÉS ÉLECTROCARDIOGRAPHIQUES.

M a l a d i e	+ 90° + 30°		+ 29° - 30°	- 31° - 90°		- 90° - 151°		- 150° + 151°		+ 150° + 90°		Nombre Total.	
	+ 90° + 30°		+ 29° - 30°	- 31° - 90°		- 90° - 151°		- 150° + 151°		+ 150° + 90°			
	+ 90° + 60°	+ 59° + 30°	+ 29° 0	- 1° - 30°	- 31° - 60°	- 61° - 90°	- 90° - 119°	- 120° - 151°	- 150° - 179°	+ 180° + 151°	+ 150° + 121°		+ 120° + 90°
Tétralogie de Fallot .....	2						3	7	3	35	122	28	200
Complexe d'Eisenmenger .....	1						2	2	1	2	14	3	25
Dextrocardio .....								2	1		1	1	4
<i>sans invers. cav.</i> .....	2			2L	1L	1L		1			1	1L	9
Atrésie tricuspidale .....	1L												
Communic. interauriculaire .....	1				2L	1L			1				2
Ventric. unique* .....				2L				1					2
Transposition vasculaire .....													3
Lévo-cardie .....													2
Trilogie de Fallot (autops.) .....											1		3
Troncus arteriosus .....													2
Sténose sous-aortique .....													3
Sténose sous-aortique complète de l'aorte (autopsiée) .....	1								1				2
Cas complexes .....				1L	1L	1	2 <sup>1</sup>		1	2	6		1
													13
	avec cyanose .....												264
Maladie de Roger .....	2	3											
<i>sans cyanose</i> .....	2L	2											
Commun. interauriculaire .....	3						1		1		2	4	12
Syndrome de Lutembacher .....													
Complexe d'Eisenmenger .....									1	1	4	4	15
Canal artériel .....	2										1	3	5
Sténose aortique .....		1									2	2	4
<i>sans cyanose</i> .....		1 <sup>1</sup>										1 <sup>2</sup>	5
Arc aortique à droite (double) .....		1											2
Cardiopathie congénitale + mitralite (RM + IM) .....	2			1	1L								1
Très gros cœur .....	1										1		3
<i>sans cyanose</i> .....													3
	sans cyanose .....												50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

50

\* Ventricule droit fonctionnant peu ou pas.  
1 Cardiopathie congénitale sûre avec mitralite (RM + IM).  
2 Canal artériel avec veine cave supérieure double vérifié à l'angiocardigraphie.  
3 Sténose sous sigmoïdienne congénitale autopsiée.  
L = sans lévogyre du vecteur.

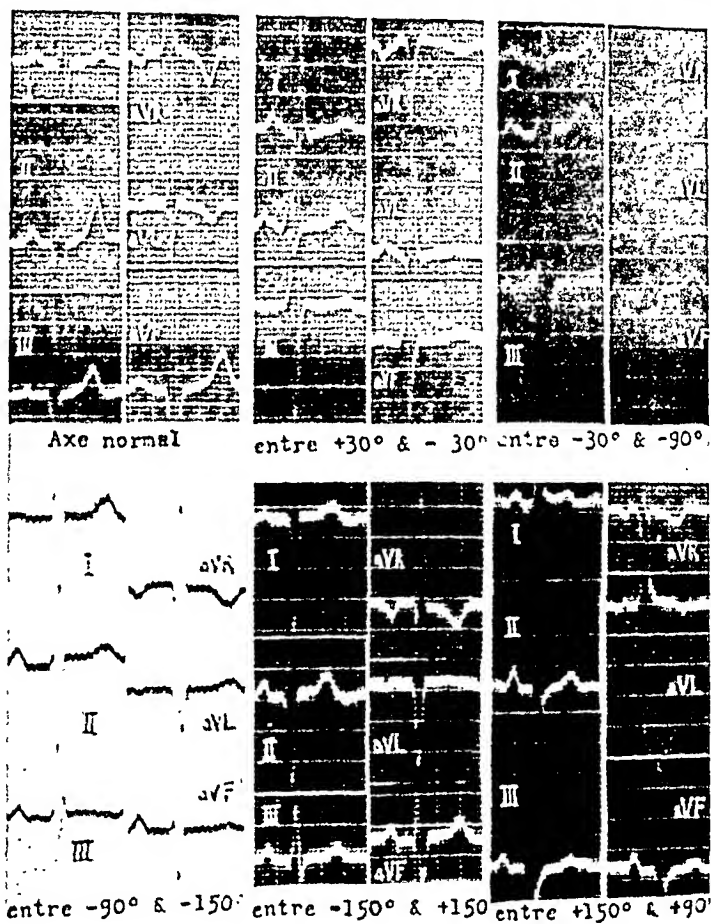


Fig. 1.

Sur les 314 tracés de cardiopathies cyanogènes et non-cyanogènes, nous trouvons donc:

25 axes normaux	(+ 30° + 90°)
15 axes déviés à gauche	(+ 29° — 90°), et
274 axes déviés à droite	202 entre + 90° et + 150°,
	51 entre + 151° et — 150°,
	13 entre — 151° et — 120°,
	8 entre — 119° et — 90°,

ces 8 derniers ayant un sens vectoriel dextrogyre; en outre, dans 2 d'entre eux, la partie la plus ample de la boucle est formée par S.

## II. Rapports entre l'axe de R, de S, du segment ST et l'onde T.

Ayant étudié séparément la situation de l'axe et l'aspect de R, S, ST et T, nous analysons maintenant le rapport de chacun de ces éléments entre eux<sup>1</sup>. Pour plus de clarté, cette étude sera faite d'après la nature de la cardiopathie.

<sup>1</sup> Nous avons confirmé les constatations de Katz et Wachtel, en ce qui concerne le diphasisme et le voltage augmenté du «complexe principal».

1°. Groupe avec cyanose: 264 cas.

1) Dans les 200 tracés de tétralogies de Fallot dont 14 autopsiées, on trouve:

- a) 2 cas avec axe moyen de QRS entre  $+ 60^\circ$  et  $+ 90^\circ$ , axe de R et de S se trouvant en place (Tétralogie de Fallot + Canal artériel),
- b) 41 cas ayant un axe de R à droite et celui de S en place dont un avec T3 négatif,
- c) 157 cas avec axe de R et de S à droite, parmi eux:
  - 52 ne présentent aucune modification de ST et de T,
  - 26 ont en plus un T3 isoélectrique,
  - 23 un T3 négatif,
  - 45 avec ST3 et T3 négatifs (dont 2 blocs de branches)
    - 2 » T2, T3 négatifs,
    - 1 » ST3 négatif et T3 isoélectrique,
    - 1 » ST3 négatif, T2 isoélectrique et T3 négatif,
    - 2 » ST3, T2 et T3 négatifs,
    - 2 » ST2, ST3 négatifs, T2 isoélectrique et T3 négatif,
    - 1 » ST2, ST3, T2 et T3 négatifs,
    - 1 » T1 isoélectrique, et, enfin,
    - 1 » T1 négatif.

En somme, sur 200 tracés de tétralogie de Fallot, nous avons trouvé 105 cas avec axe de R et de S à droite accompagnés des modifications isolées ou associées de ST et de T.

2) Dans les 25 tracés de complexes d'Eisenmenger dont 7 ayant eu une angiocardio-graphie:

- 1 fois l'axe de R et de S est normal,
- 7 » l'axe de R est à droite et celui de S en place, dont 2 avec T1 négatif,
- 17 » l'axe de R et de S sont à droite; parmi ces cas:
  - 7 sont sans altération de ST et de T (2 ont un axe moyen de QRS entre  $- 90^\circ$  et  $- 119^\circ$ ),
  - 10 sont accompagnés de modifications de ST et de T:
    - 1 avec T3 isoélectrique,
    - 8 » ST3, T3 négatifs, et
    - 1 » ST2, ST3, T2, T3 négatifs.

3) Le groupe des 13 cas de dextrocardies est plus complexe:

a) Les tracés de 4 cas avec inversion des cavités (4 vérifiés à l'angiocardio-graphie) ont été étudiés après inversion des fils. Il existe:

- 1 cas avec axe de R à gauche et celui de S à droite,
- 1 » avec axe de R à droite et axe de S en place avec ST3, T3 négatifs (bloc de branches),
- 2 » avec axe de R et de S à droite dont 1 avec ST3, T3 négatifs.

b) Les tracés des 9 dextrocardies sans inversion des cavités dont 7 opacifiées, ont montré:

- 1 fois un axe de R et de S en place pour une dextrocardie et T1 isoélectrique (axe moyen à  $+ 110^\circ$ ),
- 2 » un axe de R et de S à droite (axe moyen entre  $+ 150^\circ$  et  $- 145^\circ$ ),

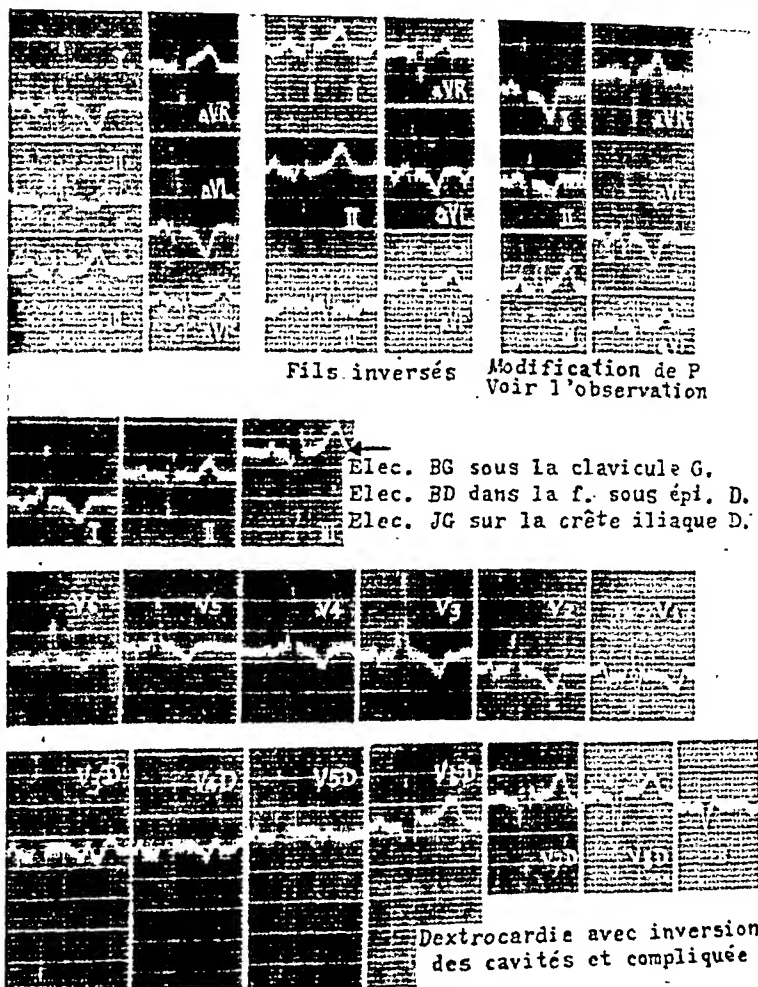


Fig. 2.

4 fois un axe de R et de S à gauche dont:

2 avec T1 négatif,

1 » T1, T2 négatifs,

1 » ST2, ST3 négatifs, T3 isoélectrique (axe moyen entre  $+60^\circ$  et  $-30^\circ$ ),

2 » un axe entre  $-60^\circ$  et  $-80^\circ$  et T1 négatif.

A propos de ces 2 derniers cas d'ailleurs opacifiés (dextrocardie sans inversion des cavités avec torsion légère du pédicule et arc aortique à gauche compliqué d'une tétralogie de Fallot), nous pouvons suggérer les notions suivantes: Dans les dextrocardies, l'axe normal se trouve entre  $+90^\circ$  et  $+150^\circ$ , tout axe se trouvant au-dessous de  $+90^\circ$  serait à gauche et celui au-delà de  $+150^\circ$  serait à droite. Si, maintenant, pour étudier la place de l'axe de QRS, nous consultons le tableau de Bayly ou de Herrmann & Wilson, nous constatons que, dans une dextrocardie, les axes entre  $-30^\circ$  et  $-90^\circ$  sont comparables à ceux se trouvant entre  $-90^\circ$  et  $-150^\circ$  c'est-à-dire à droite, dans un cœur en position normale. Cette question mérite une attention particulière.

4) Les tracés des 2 atrésies tricuspidiennes (1 opacifiée) montrent:

l'axe de R et de S à gauche dont un avec T3 négatif.

5) Dans les 2 cas de communication inter-auriculaire avec décompensation cardiaque, les tracés font ressortir: l'axe de R et de S à droite avec ST3, T3 négatifs (bloc de branche) dans un cas, l'axe de R en place mais l'axe de S très dévié à droite avec T3 négatif dans l'autre.

6) Les tracés des 3 cas de ventricule unique (2 opacifiés dont un peut-être avec oreillette unique) montrent:

l'axe de R et de S à gauche dont un cas avec T3 iso-électrique.

7) Les 2 tracés de transposition vasculaire (1 opacifiée) présentent:

l'axe de R et de S à droite.

8) Dans 1 cas de lévocardie avec tétralogie de Fallot et canal artériel (opacifié):

l'axe de R et de S était à droite.

9) Dans 1 cas de truncus artériel chez un enfant âgé de 2 ans

l'axe de R et de S est en place tandis que T1 et T2 sont très amples.

10) Dans un cas de trilogie de Fallot (communication inter-auriculaire, sténose pulmonaire, hypertrophie du ventricule droit) avec endocardite auriculaire récente et insuffisance tricuspidiennne vérifié à l'autopsie:

l'axe de R et de S était à droite, ST3, T3 étaient négatifs et P très ample sans être élargi.

11) Le tracé d'un enfant de 11 ans  $1\frac{1}{2}$  porteur d'une interruption totale de l'aorte au-dessous de l'isthme avec gros canal artériel nourrissant l'aorte descendante sans aucune communication inter-cavitaire, mais avec des cordages intra-auriculaires anormaux, hypertrophie et altération du cœur droit et surtout gauche vérifié à l'autopsie, montrait:

l'axe de R et de S à gauche (axe moyen —  $80^\circ$ ) avec flutter régulier 3/1.

12) En ce qui concerne les 13 cas de cardiopathies complexes, malgré l'angiocardio-graphie effectuée, chez 4 d'entr'eux, nous n'avons pu poser un diagnostic assez précis. Leurs tracés montrent:

l'axe de R à droite et celui de S en place dans..... 2 cas,

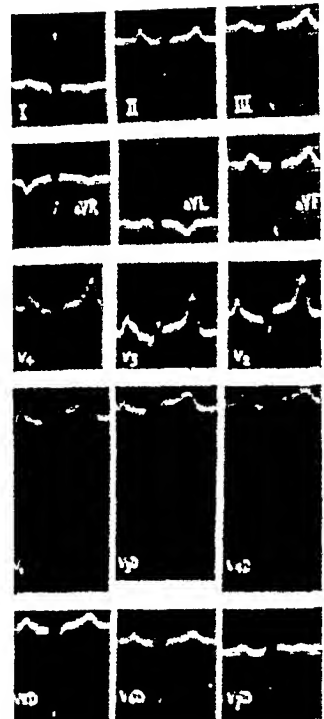
l'axe de R et de S à droite dans..... 9 cas, dont

2 avec T3 inversé,

1 » ST3, T3 négatifs,

1 » ST2, ST3, T2, T3 négatifs,

l'axe de R et de S à gauche avec ST1, T1 négatifs dans..... 2 cas.



Dextrocardie sans inversion  
cavités et compliquée

Fig. 3.



## II°. Groupe sans cyanose: 50 cas.

Nous trouvons:

### 1) Sur les tracés de 12 maladies de Roger:

- 5 fois l'axe de R et de S en place dont un avec T3 négatif,
- 5 » l'axe de R à droite et celui de S en place,
- 2 » l'axe de R et de S à droite dont un avec ST3, T3 négatifs et un avec ST2, ST3, T2, T3 négatifs.

### 2) Sur les tracés des 15 cas de communication inter-auriculaire:

- 3 fois l'axe de R et de S en place (tous opacifiés, l'un d'eux, au cours d'une tachycardie paroxystique durant trois heures, a eu une déviation de l'axe QRS à droite (+ 110°) avec l'axe de R et de S à droite),
- 2 » l'axe de R en place et l'axe de S à droite (l'un d'eux présente l'aspect typique d'un faux bloc de branches, syndrome de Wolff-Parkinson-White avec l'axe de R très légèrement à gauche).
- 3 » l'axe de R à droite et l'axe de S en place dont un avec T2, T3 très amples,
- 7 » l'axe de R et de S à droite dont:
  - 4 avec T3 négatif (1 opacifié),
  - 1 » ST3, T3 négatifs,
  - 2 » ST2, ST3, T2 et T3 négatifs.

### 3) Sur les tracés de 5 cas de syndrome de Lutembacher:

- 1 fois l'axe de R à droite et celui de S en place,
- 4 » l'axe de R et de S à droite, dont:
  - 1 avec ST3, T3 négatifs,
  - 2 » ST3, T2, T3 négatifs, et
  - 1 » ST2, ST3, T2, T3 négatifs (un de ces derniers avec décompensation cardiaque ainsi que cyanose disparue rapidement après la cure digitale).

### 4) Sur les tracés des 4 cas de complexe d'Eisenmenger:

- 3 fois l'axe de R à droite et celui de S en place dont:
  - 1 avec T2, T3 très amples.
- 1 » l'axe de R et de S à droite.

### 5) Sur les tracés de 4 cas de persistance du canal artériel (pur dont 3 opacifiés):

- 4 fois l'axe de R et de S en place, dans
  - 1 cas avec veine cave supérieure double sans aucune autre anomalie apparente, ST3 et T3 étaient négatifs.

### 6) Sur les tracés d'un cas de sténose isthmique de l'aorte:

l'axe de R et de S à gauche avec ST3, T3 négatifs.

### 7) Sur les tracés d'un cas de sténose sus-sigmoïdienne congénitale de l'aorte avec hypertrophie des deux ventricules (vérifié à l'autopsie):

l'axe normal de R et de S avec élargissement léger de QRS et T3 négatifs.

Tableau N° II.

Cas ayant un allongement de durée de QRS.

M a l a d i e	Nombre de cas analysés	Nombre de QRS au-dessus de 0''12	Durée de QRS en seconde					Segments du triaxo où est placé l'axe de R, S et T			Sons de S et de T						Type X						Unipolaires des membres thoraciques	Type de bloc																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																					
			0''12	0''13	0''14	0''15	0''16	0''17	0''18	R	S	T	S						T																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																										
													D I	D II	D III	D I	D II	D III	D I	D II	D III	D I			D II	D III																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																			
Tétralogie de Fallot	200	7	+	+	+	+	+	IV	IV	IV	I	Dex I	—	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+	D I	+

Types 1 = axe de R dévié à gauche, axe de S à gauche  
 2 = " " " " droite, " " " " " "  
 3 = " " " " normal, " " " " " "  
 4 = " " " " R à gauche, axe de S à droite  
 5 = " " " " R à droite, " " " " " "  
 6 = " " " " R normal, " " " " " "

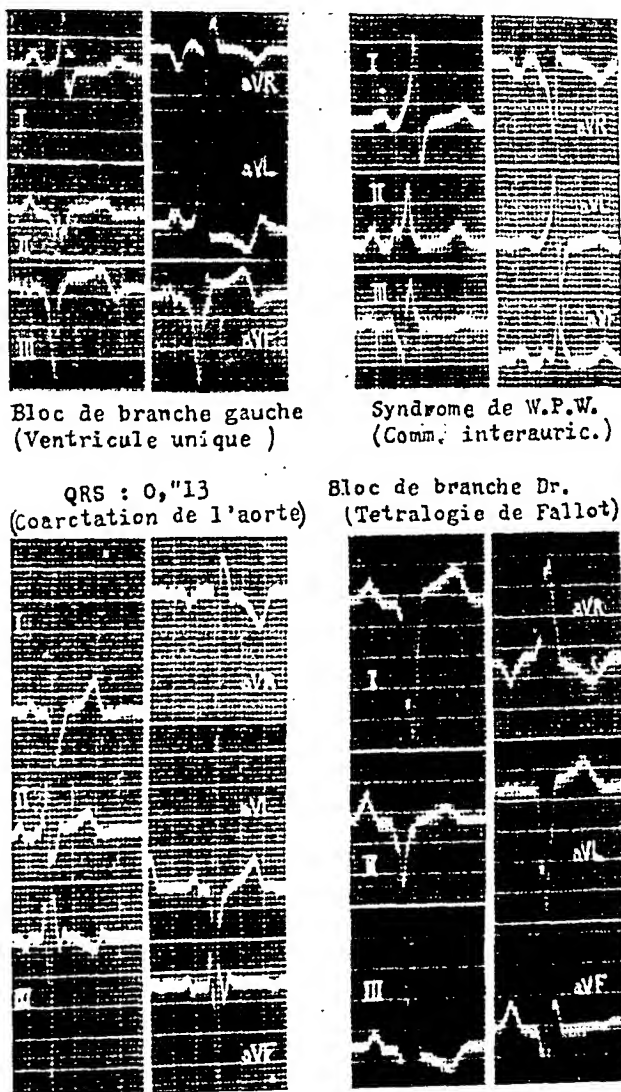


Fig. 4.

8) *Sur les tracés de l'hémicercle aortique situé à droite et sans aucune autre anomalie:*

l'axe de R en place et celui de S légèrement à droite avec ST3, T3 isoélectriques.

9) *Sur les tracés des 3 cas de cardiopathie congénitale certaine avec atteinte mitrale acquise (sténose et insuffisance mitrale):*

2 fois l'axe de R et de S en place dont un avec T1 négatif.

1 » l'axe de R et de S à droite.

10) *Sur les tracés de 2 cas de cœur très volumineux et d'un cas de cœur radiologiquement normal mais avec un souffle systolique intense:*

- 1 fois l'axe de R et de S en place,
- 1 » l'axe de R et de S à droite et ST3, T3 négatifs,
- 1 » l'axe de R et de S à gauche avec ST3, T2, T3 négatifs.

### III°. Allongement de la durée de QRS.

Nos constatations sont groupées dans le tableau II.

Parmi nos 314 cardiopathies congénitales, nous avons trouvé 21 fois un allongement de durée de QRS à 0''12 et plus qui est considéré par tous les auteurs, en particulier Burch & Winsor, Wilson & Collaborateurs, comme pathologique.

#### A — suivant l'âge:

Sur ces 21 cas, nous avons remarqué cet allongement de QRS:

- 6 fois chez des enfants au-dessous de 10 ans,
- 11 » chez des sujets entre 10 et 20 ans,
- 3 » chez des sujets entre 20 et 30 ans,
- 1 » chez un malade âgé de 31 ans.

#### B — selon la cardiopathie:

Ces 21 cas se répartissent comme suit:

- 7 fois sur 200 tétralogies de Fallot,
- 3 » » 17 communications inter-auriculaires avec petite aorte,
- 1 » » 5 syndromes de Lutembacher,
- 3 » » 3 ventricules uniques,
- 2 » » 4 dextrocardies avec inversion des cavités faisant elles-mêmes partie des 13 dextrocardies compliquées,
- 1 » » 1 sténose de l'isthme de l'aorte,
- 1 » » 1 communication directe entre les troncs artériels aortiques et pulmonaires, et
- 2 » » 13 cardiopathies complexes.

#### C — selon la durée de QRS:

Nos 21 cas ont été observés:

- 5 fois à 0''12
- 11 » » 0''13—0''14
- 5 » » 0''15—0''16
- 1 » » 0''18
- 1 » » 0''20.

#### D — suivant le type:

Pour plus de clarté et de précision, nous avons adopté la classification proposée par Zarday qui schématise les blocs de branches en six types.

Afin de préciser le siège de la localisation du bloc, et, de ce fait, la détermination de la branche lésée ou plus lésée, nous nous sommes servis de l'axe de S et non pas de celui de QRS dans son ensemble.

Nous avons trouvé dans nos 21 cas:

- 15 fois 1 bloc de branches droit,
- 4 » 1 » » » gauche,
- 1 » 1 allongement simple de QRS à 0''<sub>13</sub> (communication directe entre artère pulmonaire et aorte) et
- 1 » 1 faux bloc de branches (syndrome de Wolff, Parkinson & White (chez un sujet de 21 ans et ayant une communication inter-auriculaire certaine.

Nos 15 cas de bloc de branches droit se divisent eux-mêmes en:

- 1 cas d'hypertrophie ventriculaire gauche et bloc de branches droit (sténose de l'isthme aortique) et
- 14 » d'hypertrophie ventriculaire droite avec bloc de branches droit dont:
  - 7 tétralologies de Fallot,
  - 2 communications inter-auriculaires avec petite aorte,
  - 1 syndrome de Lutembacher,
  - 2 dextrocardies avec inversion des cavités et compliquées,
  - 2 cas avec un axe de R à droite et un axe de S en place, soit un cas de communication inter-auriculaire et un cas de malformation complexe avec cyanose, que nous croyons logique d'intégrer à ce groupe d'hypertrophie ventriculaire droite avec bloc de branches droit.

Nos 4 cas de bloc de branches gauche comprennent:

- 3 cas d'axe de R à gauche (hypertrophie gauche) tous les 3 étant des ventricules uniques,
- 1 » d'axe de R normal (cardiopathie complexe avec cyanose).

*E — étudiant le sens de T par rapport à celui de S:*

Nous constatons que, dans nos 21 cas avec allongement de la durée de QRS, le sens de T est, en général, opposé à celui de S, ainsi:

- 19 fois T<sub>1</sub> est en sens opposé à S<sub>1</sub>,
- 17 » T<sub>2</sub> est en sens opposé à S<sub>2</sub>,
- 14 » T<sub>3</sub> est en sens opposé à S<sub>3</sub>.

*F — quant au pronostic:*

- 6 de nos malades présentent une cardiopathie décompensée,
- 15 paraissent supporter leur lésion.

Nous ne pouvons tirer de ces faits aucune conclusion.

#### IV°. Modifications de l'onde P.

Nos constatations sont groupées dans le tableau III.

Il ressort que 104 de nos malades présentent des anomalies de l'onde P.

- 1 cas avec allongement simple de la durée: 0 sec. 125 (arc aortique à droite isolée),
- 95 » avec augmentation de l'amplitude de P<sub>2</sub> entre 3 et 7 mm. Ce haut voltage de P<sub>2</sub> était rarement isolé.
- 8 » avec des anomalies de l'onde P sans que l'amplitude de celles-ci en deuxième dérivation soit modifiée.

Tableau N° III.

*Allération de P dans 104 cas.*

Chiffres indiquant uniquement le nombre d'anomalies.

Maladie	Nombre de malades	Nombre d'anomalie	Durée de P2	Amplitude entre 2.5—3 & 7 mm			Isoélectrique			Inversion			Crochetage		
				P1	P2	P3	P1	P2	P3	P1	P2	P3	P1	P2	P3
Tétralogie de Fallot		63	4	18	18		1		14			13	8 &	8 &	8
					17	17					4 &	4			
					28										
Complexe d'Eisenmenger		12	1 <sup>1</sup>	8	3		1		3			1	4 &	4	
				3 &	1 &	1									
Communication Inter-Auriculaire		5	1	2 &	2				2			1			
Syndrome de Lutembacher		3		1 &	3										
					1							1	1 &	1 &	1
													1	1	
Avec invers. cav. Dextrocardie										3 <sup>2</sup>					
Sans invers. cav.		5	3		2 &	2	2	1		1 &	1		1		
					2								1		
Maladie de Roger		2							1					2 &	2
Transposition vasculaire		2			1							2			
Cardiopathies complexes					1 &	1									
					3								1 &	1 &	1
		6			2 &	2							1 &	1	
												2			
Arc aortique à droite et isole		1	1	1 &	1									2 &	2
Cardiopathie congénitale et mitralite acquise		1	1	1 &	1										
		104											1 &	1	

<sup>1</sup> Dissociation auriculo-ventriculaire complète.<sup>2</sup> Dans 2 cas P1 change de sens d'une façon passagère.

## V°. Modifications de l'intervalle P—Q.

La lecture du tableau IV.

permet de constater 20 fois un intervalle P—Q dépassant 0 sec. 20 à partir duquel il est considéré comme pathologique. Dans nos cas, cet intervalle n'a pas dépassé 0 sec. 30.

18 fois il s'agissait d'un allongement de segment PQ,  
2 » (dextrocardie) d'un élargissement marqué de P.

Six présentaient en plus des troubles de conduction intraventriculaire.

En outre, dans un cas de communication inter-auriculaire avec très gros cœur et très grosses oreillettes, PQ était particulièrement court (syndrome de Wolff-Parkinson & White).

Tableau No IV.  
Intervalle P—Q.

Affection	Nombre de cas analysés	Nombre de cas d'Interv. P—Q allongé	Durée de l'intervalle P—Q		Axe de QRS		Troubles de conduction intra-ventriculaire associés	Observations
			0.21 sec. 0.25 sec.	0.26 sec. 0.30 sec.	droit	gauche		
Fallot .....	200	12	10	2	12		2	
Eisenmenger avec cyanose .....	25	2	2		2		1	
Eisenmenger sans cyanose .....	4	1	1		1			
C.I.A. communication interauriculaire ....	17	1	1		1		1	
Lutembacher .....	5	1	1		1			
Dextrocardies avec inversion des cavités compliquées .....	4	1		1	1		1	
Dextrocardies sans inversion des cavités compliquées .....	9	1		1		1		
Malformations complexes avec cyanose non diagnostiquées .	13	1		1	1		1	

#### VI°. Troubles du rythme.

Le nombre de cas avec trouble du rythme est réduit. Par contre, la tachycardie est très fréquente. Sur nos 314 sujets, nous n'observons que 22 cas avec troubles du rythme:

6 arythmies sinusales sans valeur pathologique, et,  
16 cas (soit 4.5 %) se décomposant en:

a) — 2 extrasystoles auriculaires

- 1 tétralogies de Fallot,
- 1 communication inter-auriculaire.

b) — 8 extrasystoles ventriculaires observées dans

- 2 tétralogies de Fallot,
- 1 complexe d'Eisenmenger,
- 3 communications inter-auriculaires (dont une avec bigéminisme transitoire),
- 1 persistance du canal artériel, et
- 1 cardiopathie complexe avec cyanose.

c) — 2 flutters dans

- 1 cas de syndrome de Lutembacher, et
- 1 cas de sténose complète de l'isthme aortique avec anomalies des cordages inter-auriculaires droits vérifiée à l'autopsie.

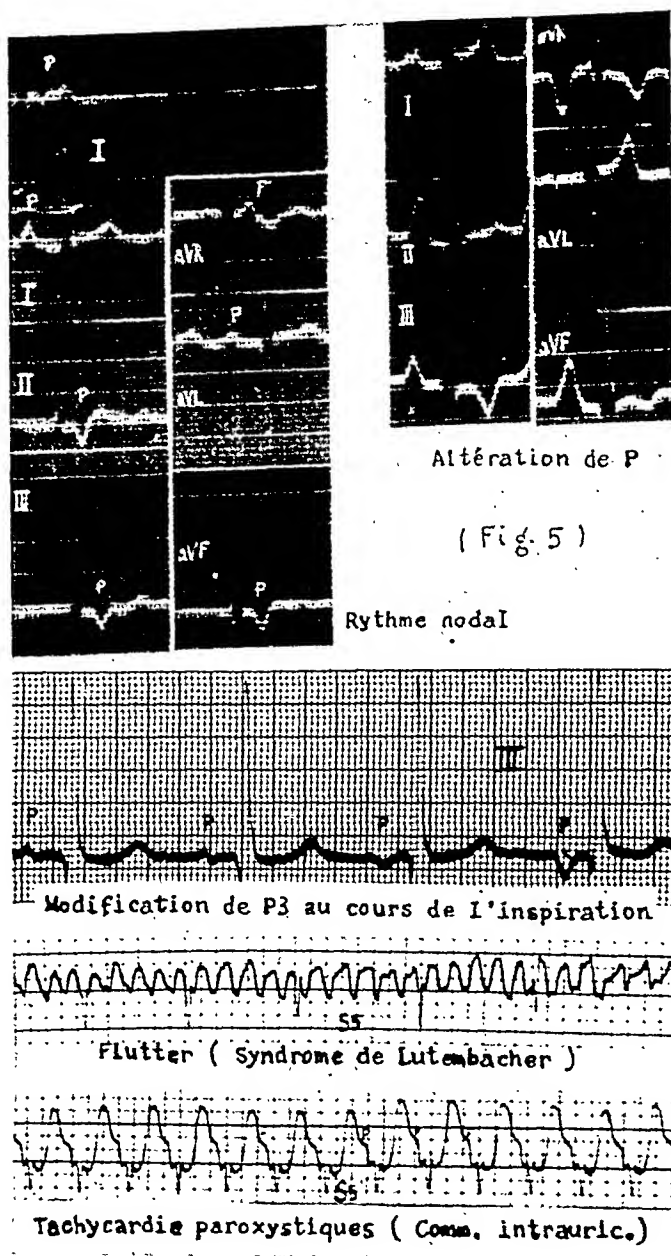


Fig. 5.

- d) — 1 rythme nodal chez une tétralogie de Fallot
- e) — 1 arrêt sinusal chez une tétralogie de Fallot
- f) — 1 crise de tachycardie paroxystique durant 3 heures dans 1 cas de communication inter-auriculaire vérifiée par l'angiocardiographie. (Fig. 5).
- g) — 1 dissociation auriculo-ventriculaire complète (Fig. 6).



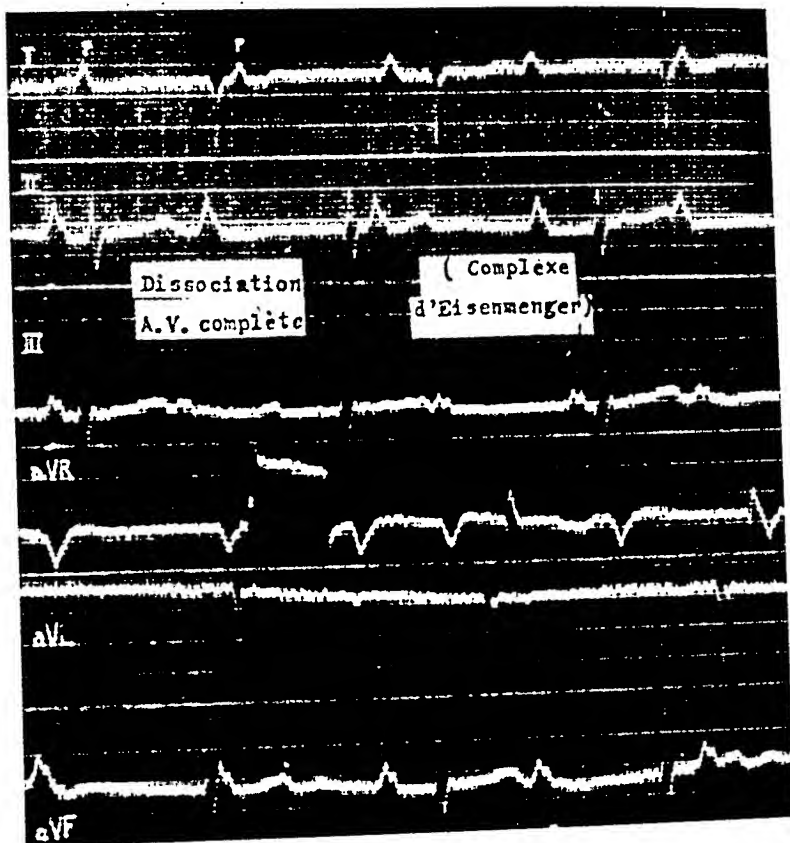


Fig. 6.

Ce cas est unique, sur nos 314 cardiopathies congénitales, il concerne un enfant âgé de 8 ans, porteur d'un complexe d'Eisenmenger.

La rareté de cette dissociation confirme les constatations anatomiques faites par Mönckeberg d'après lesquelles les anomalies congénitales des cloisons cardiaques n'entraînent pas un arrêt du développement de faisceau de HIS. Cette dissociation serait secondaire aux altérations inflammatoires surajoutées du faisceau de HIS (endocardite foetale, etc.).

### Conclusions.

De l'ensemble de ces faits se dégagent les conclusions suivantes:

La majorité des cardiopathies congénitales étudiées dans notre Centre, présentent un axe électrique de QRS dévié à droite, ce qui cadre avec les types de malformations de nos sujets.

Nous avons constaté seulement 15 fois une déviation de l'axe à gauche. Ce pourcentage est minime, mais révélateur de malformations bien déterminées.

L'étude des rapports particuliers de l'axe de R et de S montre l'importance de l'analyse séparée de chacune de ces ondes pour l'établissement de l'axe électrique.

Cette analyse détaillée révèle dans certains cas que la plus grande déflexion des ondes rapides est formée par l'onde S.

L'allongement de QRS est dans notre statistique conforme aux constatations des autres auteurs:

- les modifications de ST et de T sont fréquentes,
- les troubles du rythme sont rares (5 %), et,
- la dissociation auriculo-ventriculaire très rare. (1 cas sur 314.)

### Summary.

The authors were studying the electrocardiograms in 314 cases of congenital heart diseases among which 264 cases with cyanosis and 50 cases without cyanosis.

Among the 264 cases with cyanosis, 200 were tetralogy of Fallot.

The diagnosis was investigated in 58 cases by angiocardiology and checked by autopsy in 16 cases.

The acquired data on the limb leads were checked by the unipolar limb leads in 96 % of the cases and by multiple precordial leads in 30 % of the cases.

For each group and for each disease, the following observations will be checked:

1. Q.R.S. axis;
2. The special relations between the axis of R and of S, of the ST segment and of T;
3. The lengthening in the duration of QRS;
4. Changes in the P wave;
5. Changes in the PR interval;
6. Disorders of the heart beat.

Out of the 314 cases, it has been observed:

- 25 normal axis;
- 15 deviation to left;
- 274 deviation to right.

The changes of ST and T are frequent: in the group with cyanosis 54 % of the cases, and in the group without cyanosis 50 % have presented changes of ST and T whether isolated or connected in one or several deviations.

In 6.6 % of the cases (21 cases among which 15 with cyanosis) a lengthening of the duration of QRS to 0.12 sec. and more:

15 right bundle branch block

4 left           »           »           »

1 simple elongation of QRS (0.18 sec.).

1 false bundle branch block (Wolf, Parkinson, White syndrome).

Abnormalities of the P wave were noticed in  $\frac{1}{3}$  of the cases; lengthening of the PQ interval (over 0.20 sec.) in 6.6 % of the cases.

The disorders of the heart beat are rare: 5 %, among which, only once a congenital complete heart block.

## Bibliographie.

Battro A. & Quirino N.: El electrocardiograma en diversas cardiopatis congenitas — *Rev. Argent. de Card. Nov.*, Déc.: 335, 1935. — Burch, G. & Winsor, T.: Précis d'Electrocardiographie. Traduction française par Emam Zade A. M. Édit. Doin, Paris 1948. — Calo, A.: Deux cas de flutter auriculaire chez deux nourrissons porteurs, d'une cardiopathie congénitale. *Arch. des Mal. du Cœur* 11—12: 978, 1939. — Drawe, C., Hafkesbring, E. & Ashman, R.: Children's electrocardiograms. The changes in children's electrocardiograms produced by rheumatic and congenital heart disease. *Am. J. Dis. Childr.* 53: 1470, 1947. — Grenet, H., Joly, F. & Richard, J.: Étude électrocardiographique chez l'enfant normal. *Arch. des Mal. du Cœur* 32: 43, 1939. — Hoekenga, M. T.: Complete block in infant associated with multiple congenital cardiac malformations. *Am. J. Dis. Childr.* 69: 231, 1945. — Katz, L. & Wachtel, H.: The diphasic QRS type of electrocardiogram in congenital heart disease. *Am. heart J.* 13: 202, 1937. — Kühn, M.: Die angeborene atrioventriculäre Herzblock. *Z. Kreisl.forsch.* 34: 304, 1942. — Lepeschkin, E.: Das Elektrokardiogramm. 1942. — Mahaim, J.: Les maladies organiques du faisceau de His-Tavara (Embryologie du faisceau et malformations congénitales de cloisons cardiaques p. 516). Edit. Masson 1931. — Mannheimer, E.: The Electrocardiogram of congenital Heart defects. *Acta Paediatr.* 24: 128, 1939. — Mannheimer, E.: Calibrated Phonocardiography and Electrocardiography. A Clinical-statistical study of normal children and children with congenital heart disease. *Acta Paediatr.* 28: Supplementum 2, 1940. — Mönckeberg, J.: Die Missbildungen des Herzens in Handbuch der Speziellen Pathologischen Anatomie und Histologie. Berlin 1924: 11. Edit. Springer. — Nadrai, A.: Die Elektrokardiographie im Säuglings- und Kindesalter. *Erg. inn. Med.* 60: 688, 1941. — Pardee, H. E.: Clinical aspects of the Electrocardiograms. Edit. III, New-York. Pane B. Hoeher suc. 1933. — Pell, A. A. F.: Congenital block with atrial and ventricular septal defect. *Brit. Heart J.* 5: 11, 1943. — Prince, G. E., Ratondo, C. C. & Scott, E. P.: Auricular flutter and congenital disease. *Am. J. Dis. Childr.* 72: 552, 1946. — Rösler & Kiss: Beiträge zur Lehre von den angeborenen Herzfehlern. Elektrokardiographische Untersuchungen an 100 Fällen. *Wiener Archiv. f. inn. Med.* 21: 271, 1931. — Routier, D., Brumlik, J. & Malinsky, A.: De l'électrocardiogramme dans les cardiopathies congénitales: allongement de la durée de l'onde rapide et bloc de branches droit. *Arch. des Mal. du Cœur.* T. 33: 40, 1940. — Soulie, P., Bouvrain, J. & Bouvrain, J.: Dissociation congénitale auriculoventriculaire. *Arch. des Mal. du Cœur.* 39: 88, 1946. — Schnitker, M. A.: The Electrocardiogram in congenital heart disease. Harvard Univ. Press 1940. — Van der Klatt, A.: Congenital Bundle branch block as result probably of defect in interventricular septum. *Am. Heart J. T.* 19: 623, 1940. — Zarday, I.: Az Elektrokardiogram (elemzese es ertelmezese). Budapest 1944. — Zarday, I.: Das Elektro-Kardio-Axonogramm. *Zeitschr. f. Klinische Medizin* 140, 1942. — Yater, W. M., Leeman, W. G. & Cornell, V. H.: Congenital heart block: report of three cases of complete heart block studied by serial sections through conduction system. *J. A. M. A. T.* 102, 1660, 1934.

From the Department of Internal Medicine  
(Director: Dr. C. L. de Jongh) of the Municipal Hospital, The Hague, Holland.

## Thymol and Dilution Turbidity Tests, their Relation to the Gamma-Globulin Content of the Serum and the Morphology of the Liver Parenchyma.

By

C. K. V. VAN DOMMELEN and C. FRANCKE.<sup>1</sup>

(Submitted for publication April 19, 1949.)

The thymol turbidity test introduced by MacLagan (1) proved to be a very reliable indicator of the degree of morphological alteration of the liver parenchyma in generalized liver damage (Franklin et al., 1948), but as it depends on a disturbance of the serum proteins it is not a specific test for liver function. A positive thymol turbidity may be found in many diseases, notably in rheumatoid arthritis, lymphogranuloma venereum, heart disease, chronic pulmonary diseases, acute infectious diseases, malignancy, and in some other conditions in which no supporting evidence of liver dysfunction is apparent (Stillerman, 1948).

A simple test providing similar information has been described by Dreyfuss (4), whose «dilution turbidity test» is based on the fact that in most sera turbidity develops after the addition of distilled water.

The mechanism of the dilution turbidity test has as yet not been completely elucidated. It is possible that just as in the thymol turbidity test the turbidity depends on the presence of lipids and abnormal lipid protein complexes migrating in the  $\beta$ -globulin fraction during electrophoresis. Dreyfuss even suggests that the diluting effect of the distilled water contained in the thymol reagent is mainly responsible for the production of thymol turbidity.

In this investigation both the thymol and the dilution turbidity tests have been performed in 388 sera in order to determine whether the tests give comparable results and whether discrepancies between them have any diagnostic significance.

We also attempted to determine whether there is a relationship between the results of the turbidity tests of the thymol group (*i. e.* thymol turbidity test and dilution turbidity test) and increases in the  $\gamma$ -globulin fraction of sera. The results of the dilution and thymol turbidity tests have also been compared with the results of the Grostittation (5) carried out according to Verschure's modification (6), the

<sup>1</sup> Nèbo-Hospital, 106 Schev. w., The Hague, Holland.



laboratory of this department higher values have been only exceptionally observed in healthy persons.

In many diseases positive dilution turbidity tests were frequently found and in this respect Dreyfuss' observations were confirmed.

The thymol turbidity test and the dilution turbidity test were almost always positive in diffuse parenchymatous liver damage. Positive values were often seen in rheumatoid arthritis and more or less frequently in the following conditions: cholecystitis, cholangitis, chronic passive congestion of the liver, colitis, pneumococcal lobar pneumonia, bronchopneumonia, bronchiectasis, lung abscess, bronchogenic carcinoma, pulmonary metastases, Boeck's sarcoidosis, pulmonary tuberculosis, tuberculous pleurisy, empyema, Reiter's disease, rheumatic fever, gonococcal arthritis, gonococcal salpingo-oophoritis, syphilis, subacute bacterial endocarditis, bacillary dysentery, meningococcal meningitis, thrombophlebitis, osteomyelitis, pyelitis, chronic nephritis, hyperthyroidism, reticulosarcomatosis, multiple myeloma, Hodgkin's disease, untreated pernicious anemia and toxic hemolytic anemia.

In most patients from this series there was no reason to suspect impaired liver function, other liver function tests (when performed) had yielded normal results or the histological picture of the liver had been normal.

The comparatively small number of cases does not allow conclusions about the incidence of positive dilution turbidity tests in the conditions mentioned.

Generally the degree of turbidity in the thymol turbidity test was much higher than in the dilution turbidity test. The highest values found have been recorded in table I.

Table I.

*Highest values observed for the dilution turbidity test and the corresponding thymol turbidity values in the same sera.*

Diagnosis	DTT	TTT
Phlegmonous cellulitis	16.7	22.8
Reticulosarcomatosis	15.1	19.6
Multiple myeloma	14.6	9.0
Subacute bacterial endocarditis	13.6	14.4
Multiple myeloma	12.4	21.1
Infectious hepatitis	11.6	21.2
Lymphogranuloma inguinale	10.4	12.6
Thrombophlebitis migrans	10.0	11.0
Multiple myeloma, syphilis	9.6	12.8
Toxic hepatitis	9.4	11.0
Boeck's sarcoidosis	9.1	14.6
Convalescent from meningococcal meningitis	9.2	15.1
Tuberculous pleurisy	9.0	7.0
Uremia from nephrosclerosis	9.0	7.0
Infectious hepatitis	9.0	14.6
Subacute bacterial endocarditis	9.0	7.0
Rheumatoid arthritis	8.8	16.8
Toxic hepatitis	8.4	16.0
Infectious hepatitis	8.4	13.2
Subacute yellow atrophy of the liver	8.4	31.6
Convalescent from infectious hepatitis	8.2	18.7
Rheumatoid arthritis	8.0	14.2

In the scatter diagram (fig. 1) each point represents one of the sera investigated. The thymol turbidity values are plotted against the dilution turbidity values. The horizontal and vertical lines divide the area into 4 quadrants. All points in the left lower quadrant represent sera in which the thymol turbidity test as well as the dilution turbidity test gave normal readings (in 41 % of the total

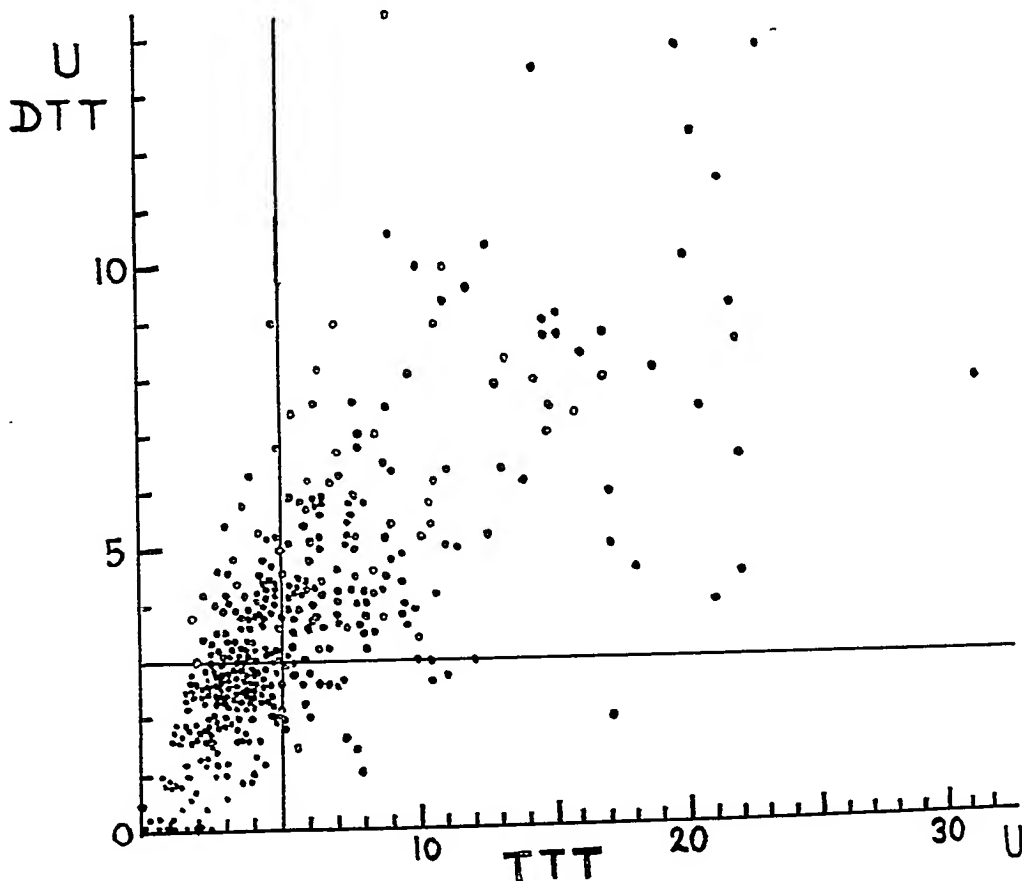


Fig. 1. The relation between thymol turbidity and dilution turbidity values.

number of sera). The points in the upper right quadrant represent sera, in which thymol as well as dilution values are pathological (in 37 % of the total). Sera showing an abnormal dilution value combined with a normal thymol turbidity are represented by the points in the upper left quadrant (17 %) and sera with a normal dilution value and a pathological thymol turbidity by points in the lower right quadrant (5 % of the total).

The scatter diagram indicates a relationship between thymol (= T) and dilution turbidity values (= D) and from the values obtained a tetrachoric coefficient of correlation<sup>1</sup> = 0.56 can be calculated while the critical ratio<sup>2</sup> is 11.0, which is highly significant.

<sup>1</sup>  $r = (ad - bc) : \sqrt{pqrs}$ .

<sup>2</sup> Critical ratio =  $t = r\sqrt{n}$ ; in this investigation the total number of sera permits all t-values of more than 2 to be considered as significant.

This correlation was also apparent in the usually simultaneous increases and decreases of the D- and T-values whenever both tests were performed at regular intervals during the course of illness in a patient.

In 22 % of the sera the results of D- and T-tests did not agree. There was no relationship between this and the nature of the pathological condition, age or sex of the patient, erythrocyte sedimentation rate, total serum protein or  $\gamma$ -globulin content of the serum and the albumin/ $\gamma$ -globulin ratio; 21 % of our sera came from patients with diseases of the liver or biliary tract and in these both tests agreed in 87 %.

Particularly in uncompensated heart disease, diabetes mellitus and in malignant disease Dreyfuss observed discrepancies between the results of D- and T-tests; 82 of our 388 sera came from such cases, but in only 10 of them the results of the D- and T-tests did not agree and therefore our conclusion might have been exactly the opposite.

In 66 cases the pathological findings were compared with the results of the turbidity tests (Table II).

Table II.

*Histopathological aspect of the liver compared with the results of dilution turbidity test, thymol turbidity test and Gros titration.*

Diagnosis	DTT	TTT	Gros titration	Biopsy or autopsy
a) Normal liver histology				
Multiple myeloma .....	0.0	0.0	0.1	A
Multiple myeloma .....	0.2	0.6	—	A
Bronchogenic carcinoma .....	0.9	3.9	0.2	A
Diabetes mellitus .....	1.0	2.6	0.8	B
Cholecystitis .....	1.0	7.8	1.0	B
Polyserositis .....	1.6	7.3	0.1	B
Cerebral arteriosclerosis .....	2.4	3.8	1.0	A
Gastric ulcer .....	2.5	1.8	1.0	A
Cholecystitis .....	2.6	4.0	0.9	B
Bronchopneumonia .....	2.8	2.6	1.0	A
Cerebral arteriosclerosis .....	3.0	2.0	1.0	A
Bronchiectasis and pulmonary tuberculosis .....	3.8	3.6	0.2	A
Polyserositis .....	4.0	9.4	0.1	A
Carcinoma of the breast .....	4.1	8.0	0.1	B
Bronchogenic carcinoma .....	4.2	8.0	0.1	B
Hodgkin's disease .....	4.2	5.4	0.1	B
Gastric ulcer .....	5.0	7.6	0.9	B
Pleural sarcoma .....	5.0	17.0	0.1	A
Embolus in the right carotid artery .....	5.2	6.4	0.3	A
Bronchogenic carcinoma and pulmonary tuberculosis .....	5.4	5.8	0.1	B
Rheumatoid arthritis .....	5.4	9.0	0.2	B
Pneumococcal lobar pneumonia .....	5.4	3.0	1.0	A
Delayed convalescence from infectious hepatitis .....	5.8	10.4	0.2	B
Tuberculous pleurisy .....	6.2	10.6	0.1	B
Convalescent from serum hepatitis .....	7.1	15.8	0.1	B
Rheumatoid arthritis .....	8.0	14.2	0.5	B
Uremia, bronchopneumonia .....	8.2	6.4	0.2	A
Convalescent from infectious hepatitis .....	8.2	18.7	0.1	B
Multiple myeloma .....	8.7	21.9	0.1	B
Subacute bacterial endocarditis .....	9.0	7.0	0.1	B



Diagnosis	DTT	TTT	Gros titration	Biopsy or autopsy
Nephrosclerosis and uremia .....	9.0	4.8	1.0	A
Erythrodermia .....	10.0	15.0	0.2	A
Multiple myeloma .....	12.4	21.1	0.1	A
b) Abnormal liver histology				
Subacute yellow atrophy of the liver				
(case 1) .....	3.0	10.0	0.1	A
(case 2) .....	4.5	22.0	0.1	A
Infectious hepatitis				
(case 1) .....	2.7	3.2	1.0	B
(case 2) .....	3.8	6.2	0.4	B
(case 3) .....	4.6	18.0	0.1	B
(case 4) .....	5.2	7.8	0.2	B
(case 5) .....	7.5	20.4	0.4	B
(case 6) .....	8.0	16.8	1.0	B
Portal cirrhosis .....	6.5	8.8	0.1	B
Fatty degeneration of the liver .....	9.6	12.8	0.1	B
Obstructive jaundice, no damage to liver cells				
(case 1) .....	0.0	2.0	1.0	A
(case 2) .....	1.9	3.0	—	B
(case 3) .....	1.9	4.1	0.1	A
(case 4) .....	2.4	2.1	0.2	B
(case 5) .....	2.4	4.8	0.1	A
(case 6) .....	4.5	2.6	—	B
(case 7) .....	5.2	4.5	0.3	A
Obstructive jaundice, inflammation of the portal triads, cholangitis				
(case 1) .....	3.4	10.0	0.1	B
(case 2) .....	3.5	8.0	0.1	B
(case 3) .....	3.5	8.3	1.0	B
(case 4) .....	5.8	5.7	0.2	B
Large metastases in the liver				
(case 1) .....	1.6	3.6	0.1	A
(case 2) .....	1.8	1.6	0.2	A
(case 3) .....	2.8	3.7	0.1	A
(case 4) .....	3.6	3.6	0.6	A
(case 5) .....	4.2	4.2	0.1	A
Heart failure, passive congestion of the liver				
(case 1) .....	1.9	2.4	1.0	A
(case 2) .....	2.6	1.9	0.3	A
(case 3) .....	3.2	3.8	1.0	B
(case 4) .....	3.8	9.0	0.1	B
(case 5) .....	3.8	9.4	0.1	A
Miliary tubercles in the liver				
(case 1) .....	6.4	4.8	1.0	B
(case 2) .....	7.6	7.6	1.0	A

In sera from patients with normal liver histology the dilution turbidity test ranged up to 3.0 in 11 cases and between 3.1 and 12.4 in 22 cases. The corresponding

figures for the thymol turbidity test were: up to 5.0 in 12 cases and between 5.1 and 21.9 in 21 cases.

In 9 cases of generalized damage to the liver cells dilution turbidity values ranged between 3.0 and 8.8 and thymol turbidity values between 3.2 and 22.0. In 7 cases of obstructive jaundice without evidence of generalized damage to liver cells the dilution turbidity values were up to 5.2 and thymol turbidity values ranged between 2.0 and 4.8.

The data shown in table II emphasize that abnormal dilution turbidity and thymol turbidity values as such should not be regarded as evidence of generalized liver damage. On the other hand, normal dilution and thymol turbidity values tend to exclude diffuse hepatocellular damage.

### Thymol and Dilution Turbidity Tests and the Gamma-Globulin Content of the Serum.

In 373 sera the dilution turbidity and formolgel tests were performed at the same time. It must be remembered that a positive formolgel reaction («Fgel +») indicates a marked increase in the  $\gamma$ -globulin content of the serum (more than 2.79 g %, the normal being about 1.95 g %). Accordingly, the formolgel test leaves an increase in the  $\gamma$ -globulin level between 1.95 and 2.79 g % uncovered.

The results may be summarized as follows: DDT + (*i. e.* more than 3.0) and Fgel + in 61 sera; DDT — and Fgel — in 159 sera; DDT — and Fgel + in 13 sera, and DDT + and Fgel — in 140 sera. Some degree of relationship is evident from these figures, the tetrachoric coefficient of correlation being 0.29 and the critical ratio 5.7, which is significant.

The corresponding figures for the thymol turbidity test (391 sera) were: TTT + (*i. e.* more than 5.0) and Fgel + in 62 sera; TTT — and Fgel — in 208 sera; TTT — and Fgel + in 16 sera; TTT + and Fgel — in 105 sera; the coefficient of correlation is 0.37 and the critical ratio 7.3, which is significant although statistically not more so than the correlation between the dilution turbidity and formolgel tests.

A positive formolgel test indicates a disorder of the serum proteins sufficiently marked in most cases to give also positive thymol and dilution turbidity tests. The probability of the thymol and dilution turbidity tests giving abnormal results increases with the increase in the  $\gamma$ -globulin content of the serum. Accordingly, a  $\gamma$ -globulin content exceeding 3.0 g % was almost always observed in combination with positive dilution and thymol turbidity tests (Table III).

An exception is shown by 3 of the 5 patients with multiple myeloma who had a considerable increase of the  $\gamma$ -globulin content of the serum. In their sera the dilution turbidity and thymol turbidity tests gave very low values. Dreyfuss observed similar results in all his 4 patients suffering from multiple myeloma. It therefore appears that the thymol turbidity and dilution turbidity tests may be of value in the diagnosis of patients suspected of multiple myeloma because of the increased  $\gamma$ -globulin content of their serum and in distinguishing this condi-

Table III.

*Dilution turbidity and thymol turbidity values in sera containing more than 3 g % of  $\gamma$ -globulin.*

Diagnosis	$\gamma$ -glob. (g %)	DTT	TTT
Convalescent from infectious hepatitis .....	3.10	7.4	15.8
Infectious hepatitis .....	3.10	9.0	14.6
Convalescent from staphylococcal sepsis .....	3.25	3.0	12.0
Toxic hepatitis, bronchiectasis .....	3.40	8.4	16.0
Convalescent from meningococcal meningitis .....	3.50	9.2	15.2
Subacute bacterial endocarditis .....	3.55	5.4	10.4
Bronchiectasis, bronchopneumonia .....	3.55	3.8	3.7
Tuberculous pleurisy, pulmonary tuberculosis .....	3.55	6.2	10.6
Subacute bacterial endocarditis .....	3.70	9.0	7.0
Allergic erythrodermia .....	3.80	10.0	15.0
Convalescent from serum hepatitis .....	3.80	7.5	20.4
Tuberculous pleurisy .....	3.90	4.2	7.0
Pneumonia, toxic hemolytic anemia .....	3.90	5.8	6.2
Convalescent from streptococcal sepsis .....	3.90	4.2	4.2
Lymphogranuloma inguinale .....	4.20	10.4	12.6
Portal cirrhosis .....	4.30	6.5	8.8
Subacute bacterial endocarditis .....	4.30	13.6	14.4
Convalescent from pneumonia .....	4.30	6.3	5.4
Boeck's sarcoidosis .....	4.55	9.4	21.6
Reticulosarcomatosis .....	4.70	8.8	14.6
Obstructive jaundice, cholangitis .....	5.00	5.8	5.7
Convalescent from infectious hepatitis .....	5.00	8.2	18.7
Rheumatoid arthritis .....	5.40	8.8	16.8
Infectious hepatitis .....	5.50	11.6	21.2
Multiple myeloma (case 1) .....	5.70	0.2	1.1
Multiple myeloma (case 2) .....	7.10	8.7	21.9
Multiple myeloma (case 3) .....	8.90	0.0	0.0
Multiple myeloma (case 4) .....	10.60	0.0	0.6
Multiple myeloma (case 5) .....	13.00	14.6	9.0

tion from chronic arthritis or chronic infectious processes which may occasionally give a clinical picture closely resembling multiple myeloma.

In table IV the results of electrophoresis of 8 sera, 5 of which showed a considerable increased  $\gamma$ -globulin content, are compared with the results of thymol and dilution turbidity tests. This series, however, is too small to justify conclusions about the mechanism of the dilution turbidity test and its relation to the  $\gamma$ -globulin content of the serum.

No relationship was observed between the results of thymol turbidity and dilution turbidity tests and the total protein of the serum. Patients who had a considerable increase of the total serum protein but without qualitative change in the serum protein pattern (*e. g.*, due to marked dehydration as a result of spastic pyloric stenosis) produced normal thymol and dilution turbidity values. In sera with a total protein content of less than 5.5 g % positive and negative thymol and dilution turbidity tests were almost equally distributed. When an increase of the total proteins was due to an increase of the  $\gamma$ -globulins (as was the case in some chronic infections and during convalescence from hepatitis or acute infections) and the patient did not suffer from multiple myeloma positive dilution and thymol turbidity tests were frequently found.

Table IV.

*Results of electrophoresis compared with dilution and thymol turbidity tests.*

Diagnosis	Total serum protein (g %)	Albumin (%)	$\alpha$ -Glob. (%)	$\beta$ -Glob. (%)	$\gamma$ -Glob. (%)	DTT	TTT
Hodgkin's disease .....	7.7	38	12	13	37	4.2	5.2
Chronic lymphatic leukemia .....	6.5	37	12	16	35	2.4	4.0
Subacute bacterial endocarditis....	8.3	35	6	14	45	9.0	7.0
Multiple myeloma (case 1) .....	11.2	26	3	8	63	8.7	21.9
Multiple myeloma (case 2) .....	12.3	16	5	6	73	0.0	0.0
Multiple myeloma (case 3) .....	14.0	16	$(\alpha + \beta =)$ 8		76	0.0	0.6
Multiple myeloma (case 4).....	11.4	34	6	10	50	0.2	1.1
Multiple myeloma (case 5) .....	5.6	64	$(\alpha + \beta =)$ 25		11	2.0	2.4

In 120 of 324 sera the Gros titration (carried out according to Verschure's modification) and the dilution turbidity test, performed at the same time, yielded abnormal values but in 83 cases both tests were negative. The dilution test was positive and the Gros titration normal (D +, Gr —) in 52 sera, but in the remaining 69 sera D — was accompanied by Gr +. The corresponding figures for the thymol turbidity test (= T) were: Gr + and T + in 101 sera; Gr — and T — in 107 sera; Gr — and T + in 32 sera, and Gr + and T — in 85 sera.

Apparently there is a relationship between the results of the thymol and dilution turbidity tests and of the Gros titration, the coefficients of correlation for dilution turbidity — Gros titration and thymol turbidity — Gros titration being 0.26 and 0.35 respectively, with the corresponding critical ratios of 4.7 and 6.3. The albumin/ $\gamma$ -globulin ratio on which the Gros titration depends (Verschure, 1948) did not apparently influence the results of the thymol turbidity and dilution turbidity tests. A positive dilution or thymol test, however, indicates that a disorder of the serum protein pattern is sufficiently gross to produce abnormal values in the Gros titration in most cases, although the latter test belongs to another group of turbidity tests.

### Comments.

Dreyfuss' dilution turbidity test was found to be a simple reaction the results of which agreed with those of the thymol turbidity test in 87 % of the sera from patients with diseases of the liver or biliary tract. Just like the thymol turbidity test, the dilution turbidity test is not specific for damage of the liver cells, but it

may provide an indicator of generalized damage of the liver parenchyma, when other conditions likely to give positive values have been excluded.

If, on the other hand, negative thymol and dilution turbidity tests are found it is improbable that widespread damage of the liver cells is present. In the presence of cholangitis both tests may produce abnormal values which, however, tend to remain much lower than in most cases of hepatitis.

In 22 % of all sera investigated the thymol and dilution turbidity values did not agree. Dreyfuss' opinion that discrepancies between the results of both tests were frequent in diabetes mellitus, uncompensated heart disease and in malignant disease, could not be confirmed.

The protein pattern in sera in which the  $\gamma$ -globulin content exceeded 2.79 g % (as indicated by a positive formolgel test) was frequently changed to such an extent that the dilution and thymol turbidity values were also found to be abnormal.

High serum  $\gamma$ -globulin levels were observed in connection with normal results of thymol and dilution turbidity tests only in multiple myeloma.

The total protein content did not by itself influence the dilution and thymol turbidity values.

The albumin/ $\gamma$ -globulin ratio was not found to be important for the results of the thymol and dilution turbidity tests, but when these tests were positive the disorder of the serum proteins was often sufficiently marked to give abnormal values in the Gros titration (which depends on the albumin/ $\gamma$ -globulin ratio).

### Summary.

In 369 sera from 316 patients suffering from various diseases the thymol turbidity test and Dreyfuss' dilution turbidity test were performed at the same time. Both tests gave results which agreed in 78 % of the whole series and in 87 % of the sera obtained from patients with diseases of the liver or biliary tract. Just like the thymol turbidity test, the dilution turbidity test may occasionally become positive in many diseases not affecting the liver.

The clinical use of the thymol and dilution turbidity tests can be stated as follows:

- a) When there is jaundice:
  1. A normal value almost certainly excludes damage to liver cells.
  2. A very high value suggests a primary liver cell lesion.
  3. Cholangitis tends to produce increased values which, however, remain lower in most cases than the values usually found in generalized damage of liver cells.
- b) When the serum protein pattern (as indicated by any screening test, *e. g.*, a high sedimentation rate, or other tests showing a marked increase of the  $\gamma$ -globulin level) is disordered, low values suggest multiple myeloma.
- c) When used as screening tests, normal values help to exclude generalized liver damage and make chronic infections less likely, but they do not exclude a serious disorder of the protein pattern such as occurs in multiple myeloma.

## References.

1. MacLagan, N. F.: *Brit. J. Exp. Path.*, 25, 234 (1944). — 2. Franklin, M., Popper, H., Steigmann, F. and Kozoll, D. D.: *J. Lab. Clin. Med.*, 33, 435 (1948). — 3. Stillerman, H. B.: *J. Lab. Clin. Med.*, 33, 565 (1948). — 4. Dreyfuss, F.: *J. Lab. Clin. Med.*, 33, 672 (1948). — 5. Gros, W.: *Dtsch. Arch. klin. Med.*, 177, 461 (1935). — 6. Verschure, J. C. M.: *Ned. Tijdschr. Geneesk.*, 92, 2027 (1948). — 7. Shank, R. E. and Hoagland, C. L.: *J. Biol. Chem.*, 162, 133 (1946). — 8. Phillips, R. A., Van Slyke, D. D., Dole, V. P., Emerson, K., Hamilton, P. B. and Archibald, R. M.: »Copper sulfate method etc.», U. S. Navy Research Unit at the Hosp. of the Rockefeller Inst. for Med. Research, 1945. — 9. Verhagen, B. A.: *Acta Med. Scand.* 132, 265 (1949). — 10. Ley, A. B., Lewis, J. H. and Davidson, C. S.: *J. Lab. Clin. Med.*, 31, 910 (1946).
-

From the Mariestad Hospital, Mariestad; the Department of Chemistry, Caroline Institute; and the Medical Clinic of the Caroline Hospital, Stockholm, Sweden.

## Intramuscular Administration of Heparin.

By

GUNNAR BAUER, M. D., HARRY BOSTRÖM, M. B., ERIK JORPES, M. D. and  
SIXTEN KALLNER, M. D.

(Submitted for publication May 5, 1949.)

When pure heparin became available for the prevention and treatment of thrombosis, it seemed natural that it should be given directly into the bloodstream, where it exerts its action. An immediate and full effect was achieved by this administration. A technique for slow continuous infusion of dilute heparin was elaborated by Murray and Best (1938), working in Toronto, and with regular checks of the coagulation time it is still used in many places. It has many advantages and the dosage can be adjusted according to the requirements of the patient. Since the individual response to heparin varies under different conditions, this technique seemed to be superior to any other.

For several reasons, however, this method was not followed by Crafoord and Jorpes (1941) when heparinization was started in Sweden on a larger scale. The supervision of continuous intravenous infusions and repeated blood examinations make such a technique too laborious as soon as a larger number of patients are heparinized. In smaller hospitals it is almost impossible to carry it out. The movement of the patient is also restricted. It became necessary to find another technique which could be used under unfavourable conditions and if possible by the private doctor. It was therefore decided to give heparin in repeated intravenous injections, *e. g.* 4 times daily. The results were encouraging and this method has since been generally used in Scandinavia. The statistics regarding the clinical use of heparin originating from the Scandinavian countries during the last few years (see Jorpes, 1946) are based on this method.

Other suggestions have been put forward, *e. g.* by Loewe and Hirsch (1947) who mix heparin powder with a specific medium (Pitkin's Menstruum) and deposit it subcutaneously. Our experience of this method was not favourable and we do not therefore intend to discuss its merits.

Following the suggestion of Dr. Neuhoef of the Mount Sinai Hospital, New York,

we decided some time ago to study the possibility of giving heparin intramuscularly. He used a 10 per cent. heparin solution. We soon found that even the ordinary 5 per cent. solution was well tolerated if injected deeply into the gluteal muscles.

### Experimental.

*The effect of the intramuscular injection of heparin on the coagulation time.*

Our first object was to study the difference in the anticoagulant effect on the blood when various doses of heparin were given intravenously or intramuscularly.

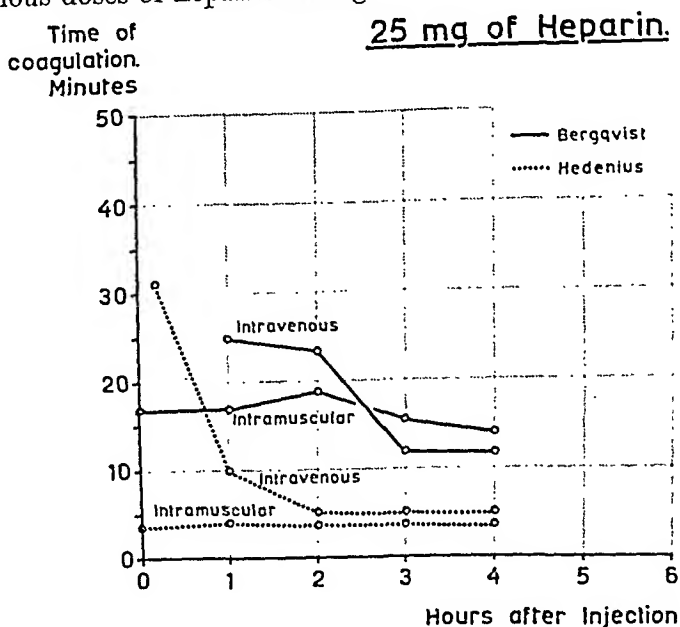


Fig. 1.

The following doses were selected: 25, 50, 75, 100, 150 and 200 mg of waterfree sodium heparinate with 100 provisional international heparin units per mg. These doses were given to 5 adults of about 70 kg body weight, patients in good general condition without any disease which might influence the results. The doses were given without correction for body weight, because differences in weight are less important than the individual differences in the intensity of the response to heparin.

For the determination of the coagulation time two different methods with a normal coagulation time of 5 minutes (Hedenius, 1937) and 15 minutes (Bergqvist, 1945) were used. The former requires venous blood in glass tubes with a moving glass bead, the latter a few drops of capillary blood on a watch glass kept moving in a closed chamber with constant temperature and humidity. We modified Bergqvist's technique by treating the watch glasses with silicones (Jaques et al., 1946) and so obtained a sensitive method with the normal clotting time at about 15 minutes against Bergqvist's 6.5 minutes without silicones.

The results are shown in Figs. 1—6 in which each curve represents the response of the individual most representative of his group.



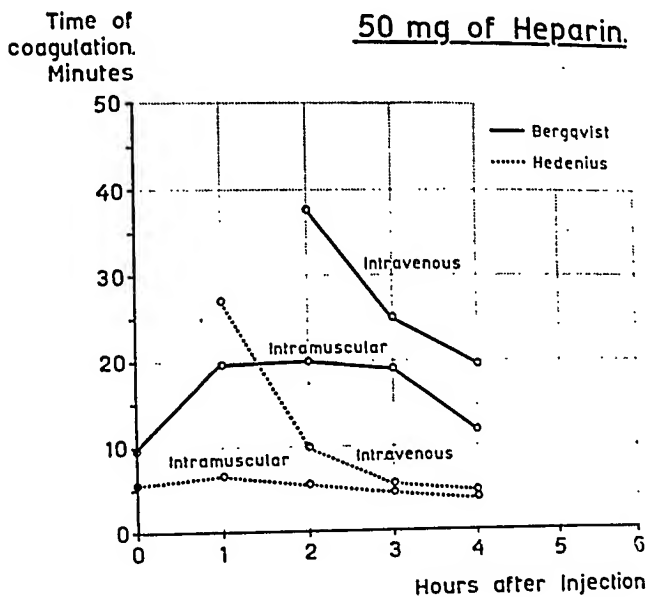


Fig. 2.

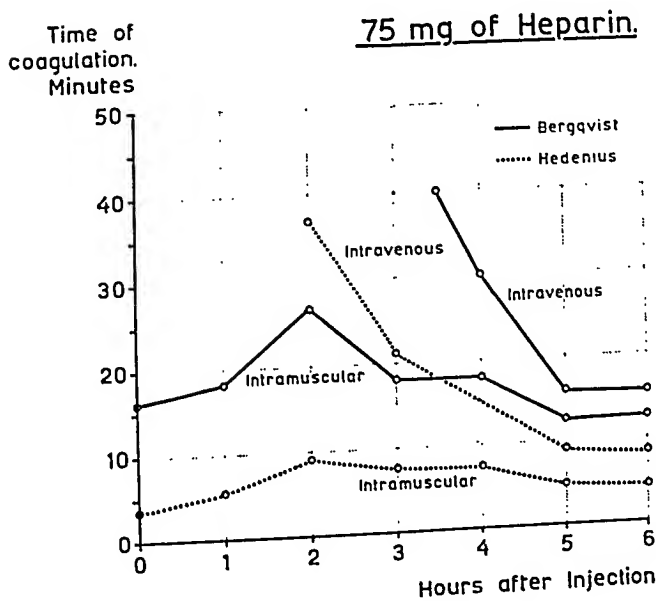


Fig. 3.

With 25 mg of heparin given intravenously there is a slight effect upon the coagulation time during the next two hours, but intramuscular administration has no effect.

After 50 mg of heparin there is an effect lasting for 3 hours even after intragluteal injection.

After 75 mg of heparin the coagulation time remains raised for about 4 hours, irrespective of the mode of administration, the curve being much higher after intravenous injection.

## INTRAMUSCULAR ADMINISTRATION OF HEPARIN.

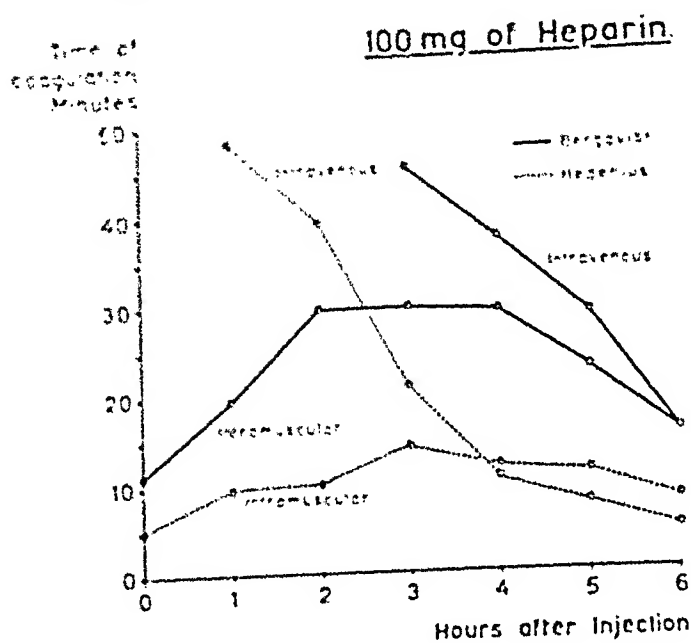


Fig. 4.

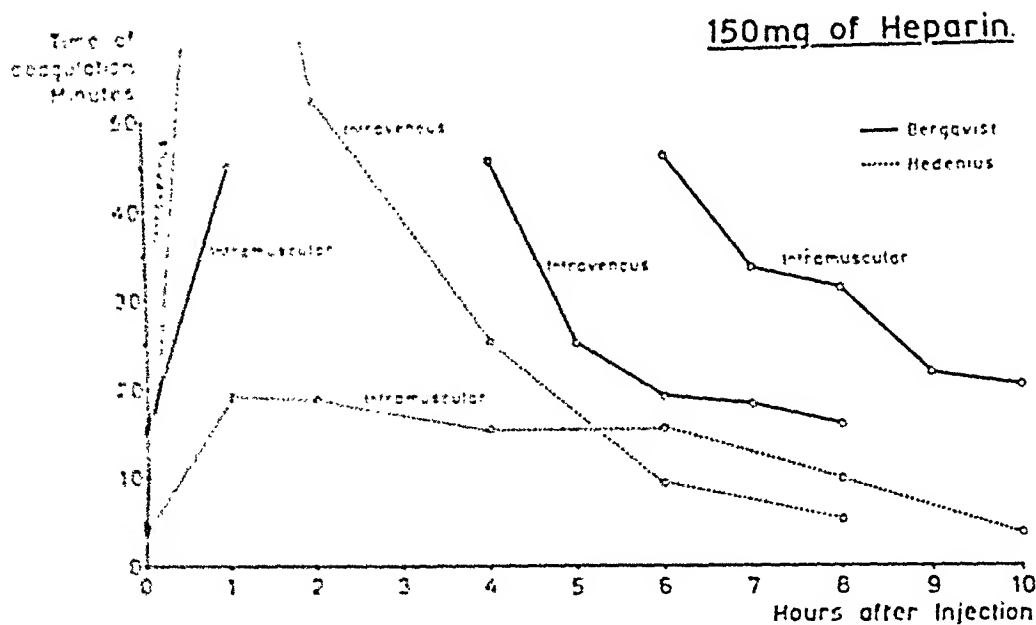


Fig. 5.

A dose of 100 mg gives an effect which lasts for 5-6 hours, irrespective of the route of injection.

The action of 150 mg can be traced for 6 hours after intravenous injection and 8-9 hours after intramuscular injection.

If 200 mg are given intramuscularly the effect lasts for 9-10 hours.

The increase in the anticoagulant effect with increasing doses of heparin given by the intravenous route is shown in Fig. 7, where the mean coagulation times

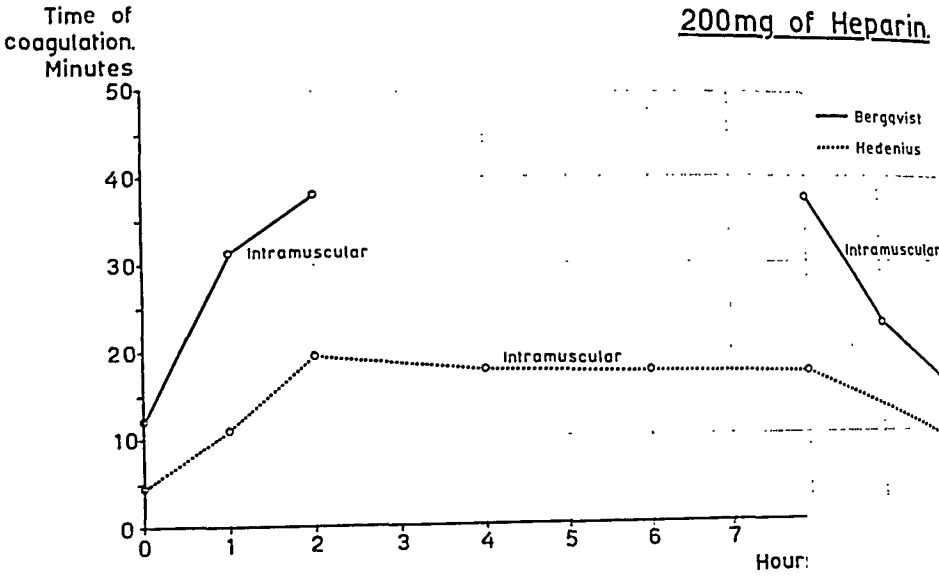


Fig. 6.

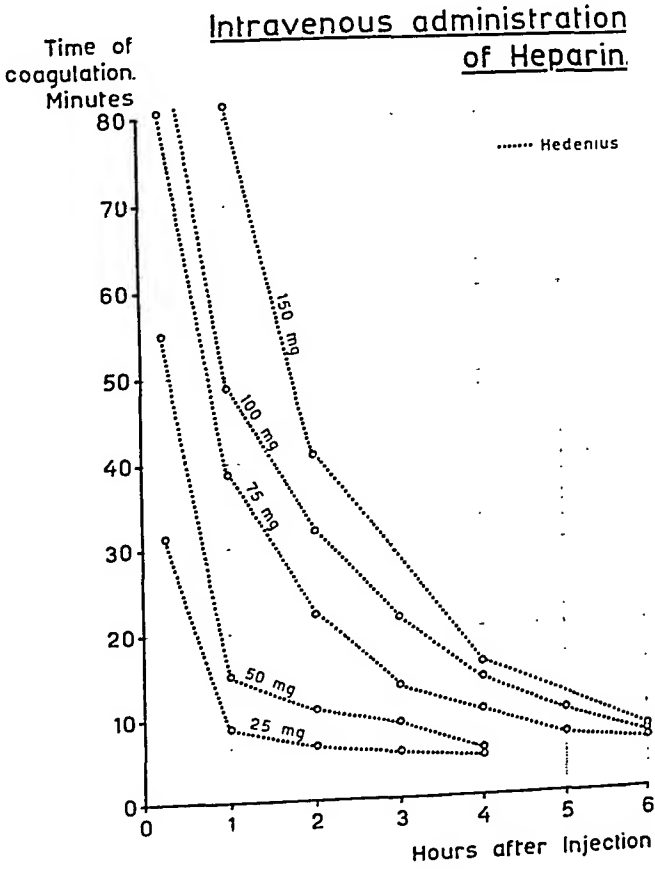


Fig. 7.

for the 5 persons in each dosage group are plotted on the ordinate against the time after injection on the abscissa. The less regular course of the curve for the 100 mg dose after intramuscular injection (Fig. 8) is due to the small number of patients in each group.

As is evident from the graphs after intragluteal administration the anticoagulant effect of heparin is only slightly prolonged. This advantage is, however, offset by the much smaller initial effect obtained during the first few hours after the injection.

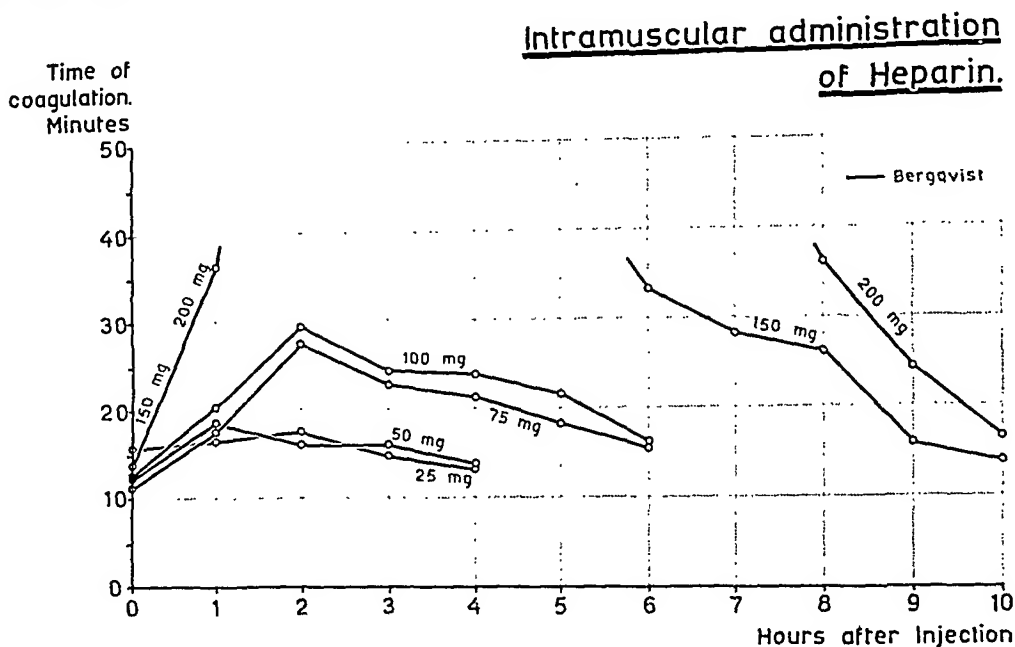


Fig. 8.

Intravenous administration gives a much more marked initial rise of the coagulation time. It is therefore possible that intramuscular injections would give a weaker effect in thrombosis. Our experience confirmed this.

### Intramuscular Heparin Therapy in Thrombosis.

Having established the facts about the effect of intragluteal injections of heparin in normal persons our next object was to study the effect on patients suffering from acute venous thrombosis. At the Medical Clinic of the Caroline Hospital a group of 25 patients and another group of 16 patients at the Mariestad Hospital were investigated. It was decided to use doses of 150 mg of heparin, given intragluteally, 3 times daily.

At the Mariestad Hospital it was possible to compare the results in 16 patients with those in a control group of 351 patients who had been treated by intravenous heparin for the last 8 years. The differences of reaction in the 2 groups are seen in Table I.

Table I.

*Comparison of methods of administration of heparin.*

	Intravenous heparin (Control cases)	Intramuscular heparin
Number of cases .....	351	16
Average amount of heparin used in each case .....	1,800 mg	2,300 mg
Average duration of hospital care after beginning of heparinization	6 days	8 days
Recurrence of the thrombotic process after reduction or cessation of heparinization .....	10 (2.8 per cent.)	7 (44 per cent.)
Fatal pulmonary embolism .....	3 (0.8 per cent.)	1 (6 per cent.)

Experience gained from a considerable number of cases of acute thrombosis studied by one of us (G. B.) and treated with *intermittent intravenous heparin*, has brought out some principles which govern the clinical course of such cases. These observations are given below together with comments on the differences observed in the patients who received intramuscular injections.

*The temperature curve* has, as a rule, a characteristic shape. There is nearly always a considerable rise in temperature on the day after the beginning of treatment and on the next day the temperature may be even higher. During the 2—3 following days the curve in most cases falls rapidly returning to normal on the 4th or 5th day.

*The pulse* is usually more rapid than would correspond to the temperature curve on the first day and when treatment is started, but afterwards soon falls and returns to normal 1—2 days before the temperature curve.

*The localized symptoms of thrombosis* in the leg also react in a characteristic way. Spontaneous pain completely disappears on the day after the beginning of treatment. Oedema also generally subsides rapidly. As a rule it is no longer apparent after 3 days. Tenderness on palpation of the deep venous trunks is somewhat slower to disappear but usually after 4 to 5 days no trace of it is left.

These facts, the characteristic temperature and pulse curves and the regression of the local symptoms, are very important when the time for the cessation of treatment must be decided. Experience has shown that on the day when both curves are normal and all palpation tenderness has disappeared the acute stage of the thrombotic process may be considered as finished. If the patient is allowed to walk with the leg bandage from then on and is given only one injection of heparin in the evening, the results are almost uniformly good. He may be discharged completely recovered 1—2 days later. Nine out of 10 patients react in this way.

*In some of the cases treated intramuscularly the clinical reactions were not so clear-cut.* The temperature curve was much slower to return to normal. In 12 out of 16 cases it was found necessary to allow the patient to get up when he was still slightly febrile. Only 9 patients had normal temperatures on discharge from hospital. The pulse rate was normal and usually followed the temperature curve closely. The local symptoms subsided more slowly than in the intravenous cases.

Most striking, perhaps, was the fact that in several instances patients found it difficult to state clearly whether they felt pain when their deep veins were palpated.

These facts made assessment of the stage of healing of the thrombotic process more difficult than in intravenously treated cases. In many cases it was necessary to stop treatment with heparin and allow the patient to get up without satisfactory evidence that the pathological process was terminated.

This may explain that many *re-activations* or *recurrences* occurred in the intramuscularly treated group. As shown in Table I there were 7 such cases (44 per cent.), while in the larger control group only 10 recurrences (2.8 per cent.) were seen.

### Fatal Pulmonary Embolism during Intramuscular Heparin Treatment.

The same difficulties in judging the regression of the thrombotic process indirectly contributed to the death in 1 case in the intramuscularly treated group. The patient died suddenly from pulmonary embolism while under heparin treatment which had been continued for 15 days, with doses considered large enough to control the vague clinical symptoms. They were, however, evidently too small.

A woman of 68 had previously been in good health.

For 5 days before admission the patient stayed in bed with a slight upper respiratory tract infection. On the third day she had a pain in the left calf which gradually became worse during the next 2 days, and the leg began to swell. Thrombosis was suspected and the patient was taken to the Mariestad Hospital.

On admission (March 25, 1948) the temperature was 37.8° C. There was moderate oedema of the left lower leg and marked tenderness on palpation of the middle and lower third of the calf, but no tenderness in the popliteal region. The upper part of the leg was normal. A diagnosis of recent deep thrombosis, involving the lower leg only, was made. Intramuscular heparin therapy was at once started, with doses of 150 mg 3 times daily.

During the following few days the temperature never rose above 38° C., but did not settle. The swelling and tenderness, however, gradually subsided and on March 30th it was considered safe to allow her to get up. She remained in the hospital for another 2 days while the temperature was still slightly raised, but because there were no longer any symptoms arising from the leg she was discharged.

The patient returned after 5 days, stating that on the evening of her discharge there was stiffness and pain in the left calf. She tried to remain out of bed, but because her temperature rose she took to her bed after a few days. Her condition deteriorated and she was re-admitted to hospital on April 6th.

She then had a temperature of 38.7° C. The whole lower leg and the *lower half of the thigh were like the "white leg" seen in pregnancy* and there was marked tenderness in the popliteal region and over the lower part of the femoral vein. The thrombotic process had evidently spread to the popliteal and lower femoral veins.

Intramuscular heparin therapy was re-commenced with the same doses. The progress was for several days similar to that observed during her first stay in hospital. The temperature remained slightly elevated. When the swelling and tenderness disappeared on April 11th it was considered safe to allow the patient to get up and gradually the amount of heparin was decreased. This was, however, followed by a slowly rising temperature and increased swelling, and the patient was again put to bed on April 14th.

During the next week the symptoms were difficult to interpret. There was a slight

swelling which disappeared for a day only to return on the next. On some days the patient complained of tenderness over the large venous trunks, but on other days she was free of pain. For some days it was felt that the thrombotic process was subsiding and the doses of heparin were decreased accordingly. On other days it was necessary to increase them again. The general impression was, however, that the process was probably about to heal.

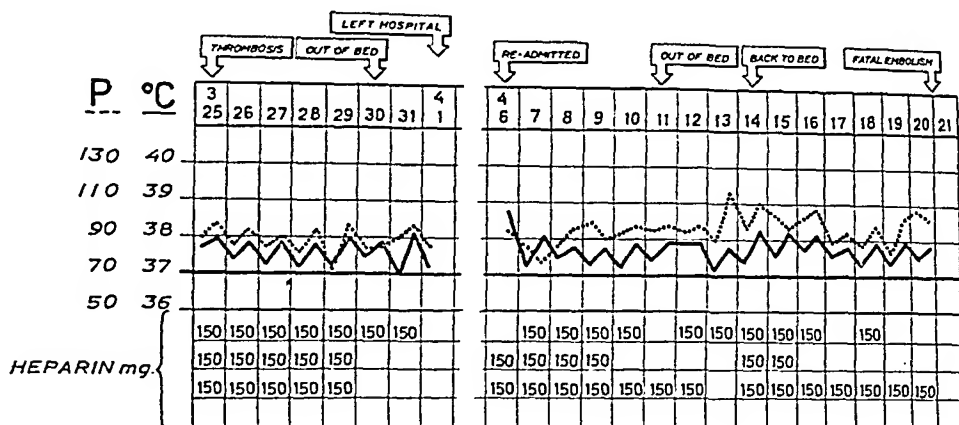


Fig. 9.

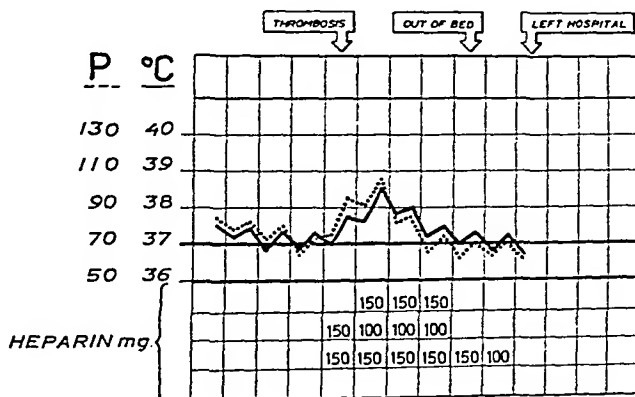


Fig. 10.

During the night between April 20th and 21st she was found dead in bed.

*Post mortem examination* showed an embolus in the pulmonary artery, about 90 cm long and 1 cm thick. The left popliteal vein and the larger calf veins were completely filled with adherent thrombi. The embolus evidently had its origin in the left femoral vein.

*Comment.* From the temperature curve (Fig. 9) it appears that the thrombotic process never ceased. For the sake of comparison the course of an ordinary early deep venous thrombosis treated with heparin intravenously is shown in Fig. 10. The course of this case was typical, the temperature returned to normal within a few days. The two figures clearly demonstrate the difference in the effect of intramuscular and intravenous heparin treatment.

*Gluteal hematoma* was observed in the series from Mariestad Hospital in 3 cases, but in only one was it large enough to cause serious inconvenience to the patient. No other complications were observed. In 4 of 25 cases from the Caroline

Hospital large intragluteal hematomata were observed, usually already on the first day.

*The mode of administration* did not cause any difficulties, although the longer and larger needles necessary caused slightly more pain and some patients complained of pain caused by the intramuscular injection. For this reason, students and nurses employed in the administration of heparin stated that they preferred intravenous injections to intramuscular administration.

### Conclusions.

The clinical course in cases of acute thrombosis indicates that intramuscular heparin therapy, with the dose employed in this study — 150 mg three times a day — does not have the same immediate and satisfactory influence upon the thrombotic process as if the same dose is given in intermittent intravenous injections.

Since studies of the clotting time show that the main difference is due to the fact that after intravenous injection the coagulation time is raised to a much higher level for 1—2 hours than after intragluteal injection, it is likely that these peaks in the curve account for the better clinical results. It seems probable that the marked physico-chemical effect of the high concentration of heparin in the blood upon the loose, newly formed clots may be the factor which influences the clinical course so favourably.

Even if intramuscular administration of heparin is easier than intravenous application, the advantage is not so pronounced and is probably offset by the fact that intragluteal administration is slightly more painful and may cause large local hematomata (in 7 of our 41 cases) and requires larger total amounts of heparin for each patient.

For these reasons intramuscular heparinization was discontinued at the Mariestad Hospital after a trial of 2 months.

In our opinion, heparin should be given by intermittent intravenous injections. Since the treatment of thrombosis aims to achieve the optimum effect at the earliest possible moment, intravenous treatment must be preferred. Intermittent injections, preferably four times a day, probably constitute the best method since the highest peaks in the clotting time curve are obtained by it. Considerable experience shows that the fall of the curve towards normal levels at the end of the intervals between injections does not matter. For this reason it is not necessary to follow the coagulation time. Though the intramuscular route cannot compete with the intravenous administration of heparin, it nevertheless remains a method for the treatment of thrombosis when intravenous injections are impracticable.

### References.

- Bergqvist, G.: Acta Chir. Scand., 92, Suppl. 101, 1945. — Crafoord, C.: Acta Chir. Scand., 79, 407, 1937. — Crafoord, C.: Acta Chir. Scand., 82, 319, 1939. — Crafoord, C.



and Jorpes, E.: J. Amer. Med. Ass., *116*, 2831, 1941. — Hedenius, P.: Lancet, II, 1186, 1937. — Jaques, L. B., Fidler, E., Feldstedt, E. T. and Macdonald, A. G.: Canad. Med. Ass. J., *55*, 26, 1946. — Jorpes, E.: »Heparin». Oxford University Press, Sec. ed. 1946. — Loewe, L. and Hirsch, E.: J. Amer. Med. Ass., *133*, 1263, 1947. — Murray, D. W. G. and Best, C. H.: Ann. Surg., *108*, 163, 1938. — Murray, D. W. G.: Surg. Gynec. Obstet., *70*, 246, 1940. — Murray, D. W. G.: Surg. Gynec. Obstet., *72*, 340, 1941. — Murray, D. W. G.: Surg. Gynec. Obstet., *77*, 157, 1943.

---

*Acta Medica Scandinavica.* Vol. CXXXVI, fasc. III, 1950.

From Kommunehospitalet, Copenhagen, III Department of Internal Medicine.  
(Director Poul Iversen, M. D.)

## Hypertensive Encephalopathy Associated with Hypochloremia.

By

TAGE HILDEN.<sup>1</sup>

(Submitted for publication April 20, 1949.)

During the last year 5 cases which were characterized by acute cerebral disturbances, hypertension and a transient fall in plasma chlorides and increases in blood urea have been observed at this department. As I could not find any similar cases in the literature the following observations are presented and they are summarized in Table I.

All the cases had hypertension and acute transient cerebral disturbances, and therefore it seems reasonable to classify them as acute hypertensive encephalopathy. In this syndrome, however, hypochloremia has not been seen, as far as could be ascertained, except in a case reported in the monograph by Iversen, Bjering and Bing (1); in this case the plasma chlorides were 245 mg%. Nor have I been able to find any transient increase in blood urea mentioned in cases of hypertensive encephalopathy, this being consonant with the old nomenclature, pseudouremia, which indicate the absence of azotemia.

Low plasma chlorides and increased blood urea values are well known in cases of chronic glomerulonephritis at the stage where patients loose their salt in the urine. This diagnosis must therefore be considered in our cases. The laboratory findings and the course of the illness, however, did not resemble those in chronic glomerulonephritis and the electrolyte disturbances seen in cases of chronic glomerulonephritis are of a more protracted character and do not remit spontaneously nor are they necessarily connected with acute encephalopathy. Two of the cases must, however, be diagnosed as chronic pyelonephritis (cases 3 and 4).

As vomiting is a feature of acute hypertensive encephalopathy the possibility had to be considered that the hypochloremia found here was due to vomiting. There can be no doubt that to some extent this did happen. For the following reasons, however, I do not think that the hypochloremia could be accounted for

<sup>1</sup> Hovedvej 61, Glostrup, Denmark.

Table

No.	Sex	Age	History	Vomiting
1	F	75	Mild diabetes for 6 months. Sudden blindness, admitted to ophthalmic department, transferred to medical department.	No
2	F	72	Hypertension for several years. 10 days before admission complained of dizziness.	No
3	F	61	10 years ago acute pyelonephritis. 5 days before admission increasing headaches and dizziness.	++
4	F	39	24 years ago acute nephritis. For the last years headaches; recently nausea and blurring of vision.	(+)
5	F	43	Cardiac symptoms for the last years. 1 day before admission severe headaches and drowsiness.	(+)

No.	Ophthalmoscopy Keith & Wagener	Plasma chlorides in mg per 100 ml		Plasma CO <sub>2</sub> in vol %		Blood urea in mg per 100 ml	
		On admission	Later on	On admission	Later on	On admission	Later on
1	III	230	340	60	70	163	19
2	II	310	345	64	74	84	32
3	II	305	385	75	70	56	36
4	II	310	360	52	86	42	27
5	III	300	(320)	62	67	46	21

exclusively by vomiting: (1) some of the patients vomited little or not at all, (2) hypochloremia due to vomiting is usually connected with alkalosis, but in our patients the plasma CO<sub>2</sub> values were normal with a tendency to increase as the plasma chlorides reached normal levels. Only in one case (No. 3) did the plasma CO<sub>2</sub> values decrease and this was the only patient who vomited repeatedly.

The plasma sodium was not estimated, but from the normal values for the plasma CO<sub>2</sub> it seems reasonable to presume that a decrease of the plasma sodium took place simultaneously with the decrease in the plasma chloride. We must assume therefore that an increased excretion of sodium chloride occurred, probably through the kidneys.

On admission	Blood pressure		Urine	
	On admission	Later on	Protein	Microscopy
Blind Drowsy; not paralysed.	290/160	175/100	+	normal
Only complaint: dizziness.	240/130	160/100	absent	normal
Drowsy, not paralysed.	190/130	140/80	(+)	many white blood cells
Only complaint: headaches.	240/180	175/100	+	many white blood cells
Almost unconscious, but very restless. Transitory left hemiplegia.	250/150	180/90	+	normal

Treatment	Diagnosis	Course of illness
Saline, subcutaneously	Diabetes mellitus. Malignant hypertension	Some improvement of the mental state; later on cerebral hemorrhage with hemiplegia. Death after 4 months; autopsy refused.
Symptomatic	Essential hypertension	Discharged without complaints.
Saline, subcutaneously	Chronic pyelonephritis	Discharges with only minor complaints.
(Streptomycin for urinary infection)	Chronic pyelonephritis	Discharged with slight headaches.
Saline, subcutaneously. (Later on thyroidectomy)	Essential hypertension Hyperthyroidism.	One day after admission the patient was transferred to psychiatric ward; returned 2 days later. Later on hyperthyroidism was discovered. After thyroidectomy discharged with slight cardiac complaints.

The transient increase of the blood urea may be explained as a consequence of the decrease in the plasma chlorides although definite evidence for this is lacking.

The object of this report is to draw attention to the alterations in the plasma chlorides and blood urea values. These should be investigated in all cases of acute encephalopathy. The relationship between electrolyte disturbances and cerebral symptoms have got a new actuality from the now very widely used treatment of hypertension by a salt-poor diet. With sodium chloride restriction, however, the result may be marked hypochloremia and an increase of the blood urea, and cerebral symptoms or even death may follow (2, 3).

In this series 3 cases were treated with parenteral saline and I believe that this improved their condition. This treatment is therefore suggested for hypertensive encephalopathy with hypochloremia.

### Summary.

Five cases of acute hypertensive encephalopathy with a transient decrease in plasma chlorides and an increase in blood urea are reported.

Three cases improved with parenteral administration of saline.

### References.

- 1) Iversen, Bjerling & Bing: De medicinske Nyrelidelser, Copenhagen, 1946. — 2) Kempner, W.: Personal communication; 1948. --- 3) Macguire, W. B.: J. A. M. A. 137, 1377; 1948.

From the Radium Centre in Copenhagen.  
(Director: Jens Nielsen.)

## The Course and Prognosis of Hodgkin's Disease.

By

AAGE VIDEBÆK.<sup>1</sup>

(Submitted for publication May 18, 1949.)

Since the introduction of X-ray therapy the treatment of Hodgkin's disease has become established because granulomatous tissue proved to be extremely radio-sensitive, but though X-radiation often produced marked immediate improvement of the condition, it remained doubtful, whether it really did delay death and improve the prognosis. Prognostic studies have shown that there is no doubt about the symptomatic as well as prognostic importance of X-ray therapy as shown by the reviews by *inter alia* Leucutia (1934) and Gilbert (1939). The increase in the average duration of the disease is no doubt partly due to improved technique and partly to more careful observation of the patients, involving treatment at a time more favourable during the disease, while no new therapeutic measures have been adopted.

At present drugs are being introduced which, administered in one way or another, may have a more or less universal effect closely resembling to or identical with the effect of X-rays. It is therefore useful to consider what can be achieved by the therapeutic measures currently available, so that one is not struck with too much amazement at the effect of new chemotherapeutic agents like nitrogen mustard on the granulomatous tissue. The results of a therapy which has been thoroughly tested and which required a long time to be developed to its present level should not be forgotten, though its efficacy leaves much to be desired.

### Material.

During the period 1930—45 a total of 172 patients, 90 males and 82 females, with Hodgkin's disease have been treated at the Radium Centre in Copenhagen. The predominance of males is not as striking as in other series (*e. g.* Goldman, 2.1 : 1; Slaughter & Craver, 1.6 : 1; Minot & Isaacs, 1.8 : 1). Only 3 of the patients were children, and the fact that all were boys is probably not due to chance.

<sup>1</sup> Rigshospitalet, Copenhagen (Denmark).

Slaughter & Craver (1942) among others, reported a marked predominance of boys (12 : 3). According to information kindly supplied by the National Health Service of Denmark 44 persons below the age of 15 years died of Hodgkin's disease during the period 1935—47; of these 33 were boys and only 11 girls.

### Diagnosis.

The diagnosis was confirmed in all cases by histological examination. Doubtful cases have been excluded. Autopsy was performed in 46 cases (32 per cent of all deaths). On the basis of this series which was followed up until the end of 1948 the prognosis was studied in a series of patients who were exclusively treated by X-ray therapy which was carried out on uniform lines. The shortest observational period was 3 years, but most of the patients were followed up much longer, up to 13 years. During the course of the disease most patients were controlled at the Out Patient Department of the Radium Centre.

### Age Distribution.

This is shown in Fig. 1. It agrees with that recorded by other workers but the curve differs considerably from the one usually considered to represent malignant growths which describes an evenly ascending line and a steeper descending line. This course has been explained in the way that several individuals of the older age groups die from intercurrent diseases before they develop cancer. Hodgkin's disease, on the other hand, usually occurs at a time of life when this phenomenon plays no considerable part, and the age distribution of the disease is practically a mirror image of the curves for cancer in the older age groups. The disease may, however, occur at any age. The average age at the time of the first symptom is 34 in males and 33 in females, in our series.

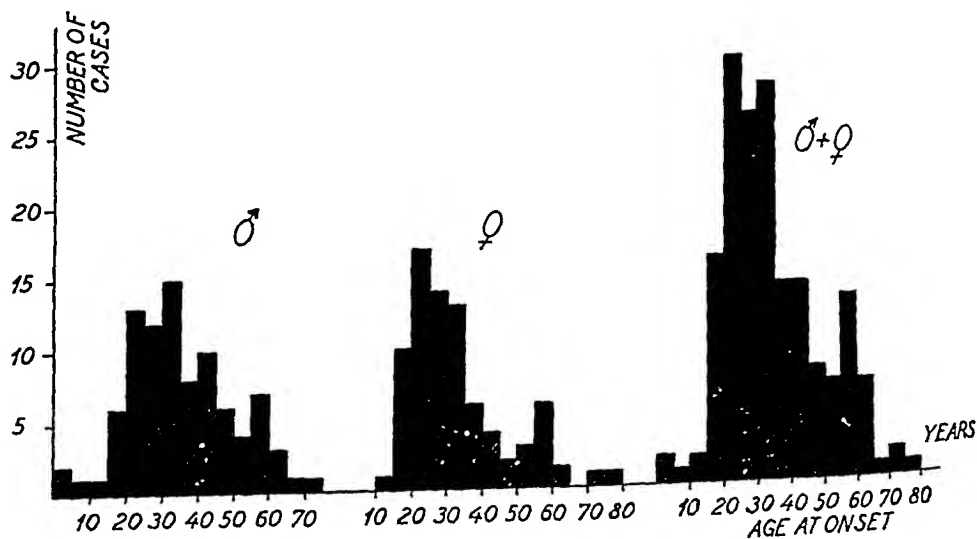


Fig. 1. Age distribution among 90 males and 82 females with Hodgkin's disease.

### Causes of Death and Co-existent Diseases.

At the time when this study was concluded only 29 of the 172 patients were alive. On the basis of the Danish statistics of the causes of death, it can be calculated that among 172 persons chosen at random, with the same age and sex distribution as the 172 patients with Hodgkin's disease, about 2 per cent (or about 4 patients) should have died during the course of  $3\frac{1}{2}$  years (the average duration of the disease), when all causes of death are considered. Actually only 5 patients died from other diseases, *i. e.* 3 from tuberculosis, 1 in hepatargy and 1 from heart disease. Particularly interesting was a man of 55, who had an operation for squamous cell carcinoma of the penis 1 year before the diagnosis of Hodgkin's disease, but a man of 23, had an intestinal neurocytoma, and a man of 39, an oesophageal fibromyoma. Two patients also suffered from diabetes mellitus.

### Treatment.

Treatment was modified in the individual cases, but the main principles were the same. Before the treatment a biopsy was made if at all possible. The treatment of the first foci was started as soon as possible with daily doses of usually 100—200 r (up to a total of 500—1500 r, depending on the effect, region and tolerance),  $\frac{1}{2}$  mm Cu., focal-skin distance 40—60 cm. The patients were usually seen at 3—6 months' intervals, and the appearance of new foci or recurrences were controlled by thorough clinical examinations, X-rays of the skeleton and mediastinum, and blood examinations. Prophylactic treatment of exposed regions was not used. When there was fever or when the general condition was poor, the treatment was stopped or continued with particular care. In generalized cases universal radiation with 5 r at a time was sometimes tried, often with some success, but as a rule the effect on such patients was doubtful. When the general condition was poor, the temperature of a septic type, or when there was severe anemia, the treatment was often supplemented with blood transfusions.

Although the results of this individualized treatment with frequent search for new foci leave much to be desired, some success has no doubt been obtained. The results are similar to those reported by other workers (Table 1).

Table 1.

*Results obtained by various authors in the treatment of Hodgkin's disease.*

A u t h o r s	Average duration of the disease	5-year sur- vival	Number of patients
Dejardins & Ford (1926) . . . . .		10 %	135
Holfelder & Hummel (1932) . . . . .	3 yrs. 5 months	18 %	52
Craver (1934) . . . . .		17 %	125
Pendergras (1934) . . . . .		15 %	
Gilbert (1939) . . . . .	$4\frac{1}{2}$ years	34 %	73
Slaughter & Craver (1942) . . . . .	2 yrs. 10 months	29 %	265
Jackson & Parker (1947) . . . . .		25 %	262
Present series . . . . .	$3\frac{1}{2}$ years	28 %	172



### Course and Prognosis.

The disease is insidious, the acute cases being extremely rare (only 7 of the 172 patients died in less than 6 months). The average duration among the males was a minimum of 3.3 years and among the females a minimum of 3.8 years. Variations, however, are wide (from 2 months to 13 years), and the average survival time affords little information about the individual prognosis. Jackson & Parker rightly state that »the individual patient is not the average one». This is perhaps

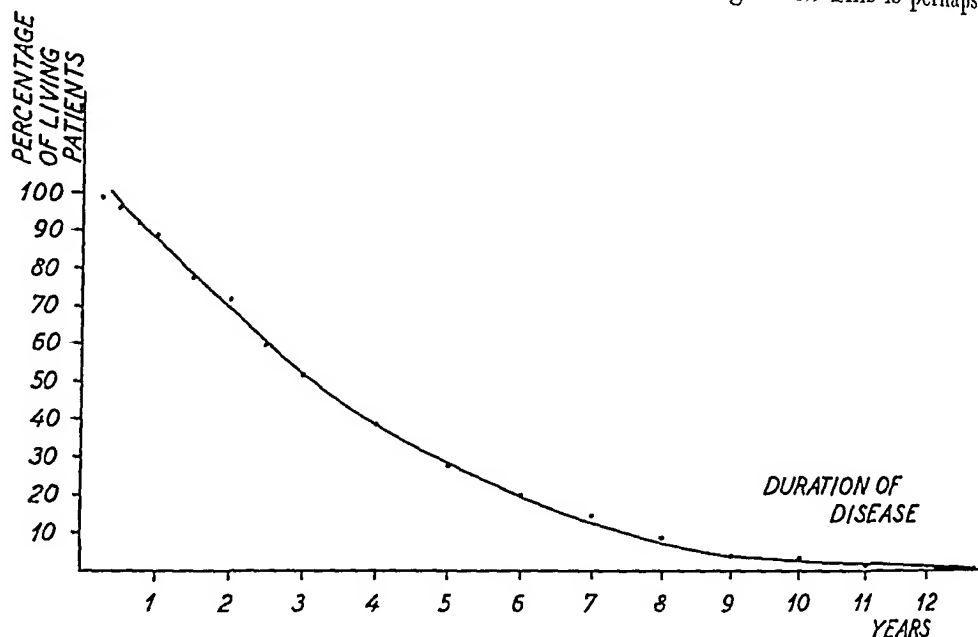


Fig. 2. Survival rate — calculated from the onset of the first symptom of 172 patients with Hodgkin's disease (29 are still alive).

best illustrated by the graph representing the survival rate (Fig. 2) showing how many per cent of the 172 survived after a follow-up period of up to 13 years. Half the patients were dead in about 3 years,  $\frac{3}{4}$  in about 5 years, but after 6 years about 20 per cent of the patients were still alive and after 10 years 3—4 per cent.

The survival rate is the same for males and females and the prognosis is therefore the same for both sexes. This agrees with the observations of Slaughter & Craver (1942), but Epstein (1939) maintained that the prognosis was better for females. The prognosis is not particularly poor in children. In our series there were 3 children whose illness commenced at 3, 4, and 7 years of age and lasted 3,  $5\frac{1}{2}$ , and  $5\frac{1}{2}$  years respectively.

Table 2 shows the prognosis for patients of various ages assessed on the basis of the average duration of the disease among young and old patients. The average duration for all the younger age groups is almost 4 years and a little longer for children, but in the oldest group of patients — more than 60 years of age — the disease runs a much shorter course, probably because of the generally reduced resistance in advanced age. Age, however, is not always tantamount to a par-



were only 3), but worst for patients of over 60, and there was no sex difference in this respect.

The survival rates are set out in a diagram. Five years after the first symptom 28 per cent of the patients were alive but after 10 years about 3 per cent only.

#### References.

Craver, L. F.: *Amer. J. Med. Sci.*, 188, 609, 1934. — Dejardins & Ford: Quoted by Gilbert. — Epstein, E.: *Amer. J. Cancer*, 35, 230, 1939. — Gilbert, R.: *Amer. J. Roentgenol.*, 41, 198, 1939. — Goldman, L. B.: *J. A. M. A.*, 114, 1611, 1940. — Holfelder & Hummel: Quoted by Gilbert. — Jackson, H. & Parker, F.: »Hodgkin's Disease and Allied Disorders». Oxford University Press, N. Y. 1947. — Krumbhaar, E. B.: »Symposium of the Blood and Blood-forming Organs». University of Wisconsin Press, 1941. — Leucutia, T.: *Amer. J. Med. Sci.*, 188, 612, 1934. — Minot, G. K. & Isaacs, R.: *J. A. M. A.*, 86, 185, 1926. — Pendergras: Quoted by Krumbhaar. — Slaughter, D. P. & Craver, L. F.: *Amer. J. Roentgenol.* 47, 596, 1942.

---

From Pratolino's Sanatorium, Florence, Italy.  
(Head: Prof. S. Aloigi-Luzzi.)

## Concentrations of Dihydrostreptomycin in Blood, Serum and Urine, Increased by Solution in Procain-Pectine.

By

FRANCESCO ZINI, M. D.

(Submitted for publication April 11, 1949.)

After parenteral administration the concentration of streptomycin in the blood rapidly reaches its maximum and it is quickly completely excreted by the kidneys (1, 2, 3, 4). The behaviour of dihydrostreptomycin in the human body is very similar to that of streptomycin (5, 6, 7).

According to Waksman (8) the dose of streptomycin necessary to inhibit in vitro the growth of the human strains of *Myc. tuberculosis* is 0.15 S. U. per ml. According to Rake, Pansy, Jambor and Donovick (9) the minimum concentration in vitro is 2 mg per ml for the strain H37 Rv and 0.52—1 mg per ml for the strain of *Myc. tuberculosis* isolated from tubercular sputum. The dose of antibiotic necessary to produce in vivo a bacteriostatic effect on the tubercle bacillus is much higher than the dose necessary for the inhibition in vitro. According to Canada (10) level of streptomycin in the serum of 17.5 mg per ml proved to be bacteriostatic in vivo.

Hobson, Tompsett, Muschenheim and McDermott (5) maintain that after the intramuscular administration of 1—1.18 g of dihydrostreptomycin or streptomycin in isotonic solution the antibiotic level one hour after its administration was 40—70 S. U. per ml of serum (see Fig. 1); in the 4th hour the serum level of the antibiotic varied from 23—16 mg per ml; between the 8th and the 12th hour the serum concentration was just below the lower limit required for bacteriostasis. This corroborates the knowledge which is already known that it is necessary to administer doses of antibiotics every 3—4 hours when bacteriostatic blood levels are required. According to Levin, Carr and Heilman (11) 1 g of dihydrostreptomycin produces a concentration of 1.05—1.75 mg per ml in the serum in 24 hours.

Rake, Pansy, Jambor and Donovick (9) report that in cats which had a dose of 200,000 S. U. of streptomycin injected, the antibiotic level in the blood was of

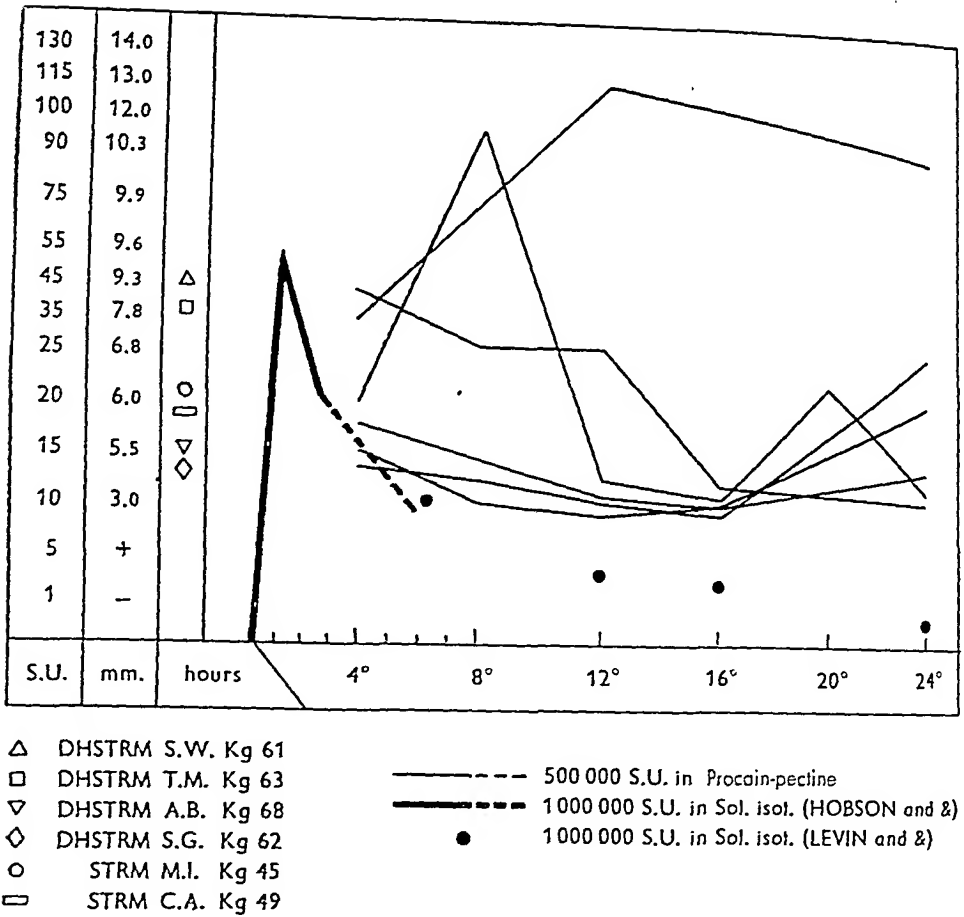


Fig. 1. Concentration of Dihydrostreptomycin and Streptomycin in serum after a unique intramuscular administration of g 0.50 (500.000 S. U.) in Procain-Pectine 2 %.

90 S. U. after 30 minutes, 25 S. U. after the first hour and 5 S. U. after the second hour, but after 3—4 hours only traces were detected. In the urine collected during the 4th hour a quantity of antibiotic is found which added to the quantities found in the urine excreted during the first 3 hours seems to account for the total dose administered. So far only antibiotics specific against tuberculosis diluted in isotonic solution have been discovered.

This note aims to correlate for the first time the behaviour of dihydrostreptomycin and streptomycin diluted in pectine and to consider the concentration of antibiotic in the serum, in whole blood and in the urine.

For the biological titration of the antibiotic the method of an agar plate with a few holes has been used. It was employed by Fleming in order to show the bacteriostatic action of lysozyme on certain bacteria. Some minor variations of the original technique have been made and the method followed in this research is described here.

Plates of 12 cm in diameter are used; at the bottom of the plate 2 drops (0.1 ml) of broth culture of staphylococcus aureus 131 are placed; 40 ml of beef extra

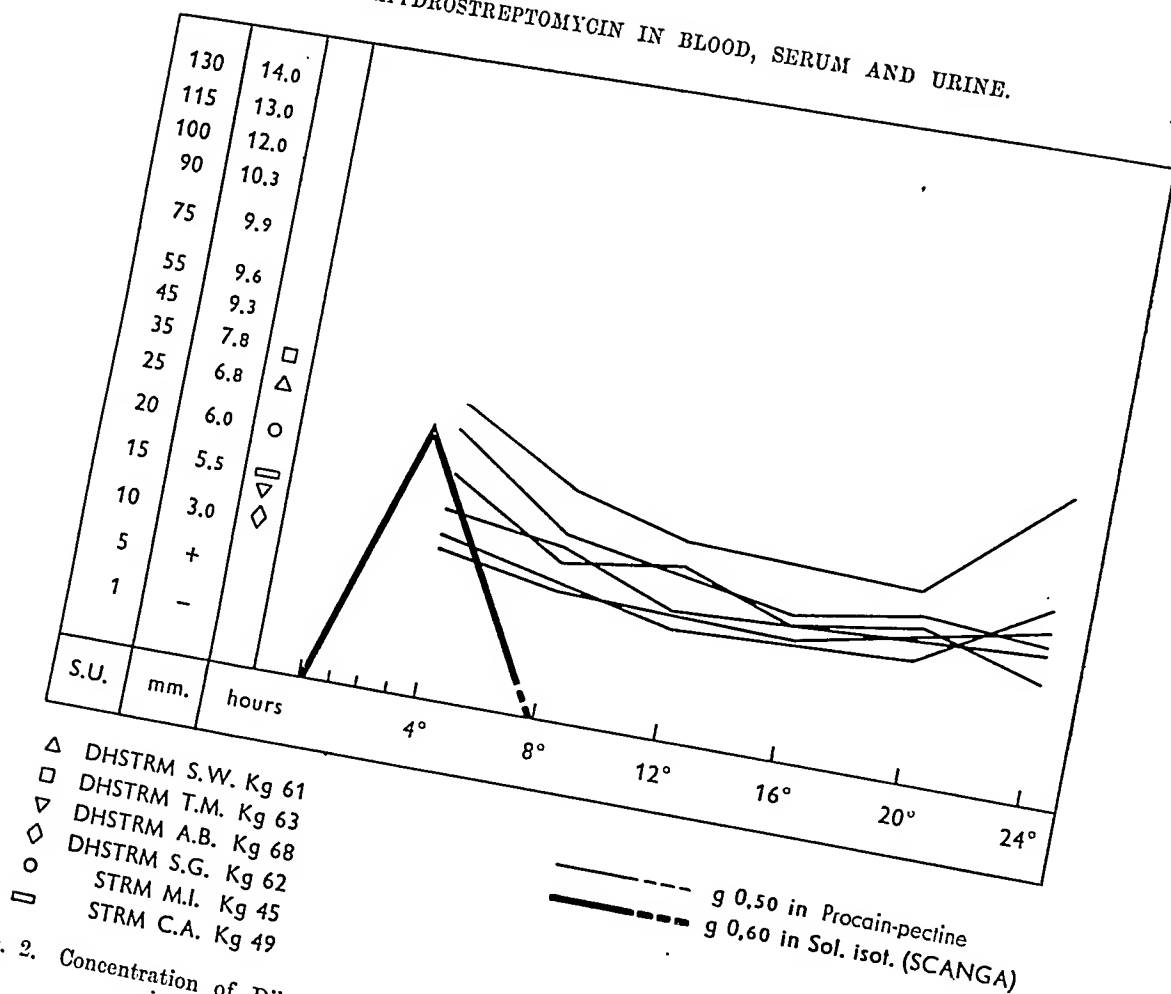


Fig. 2. Concentration of Dihydrostreptomycin and Streptomycin in whole blood after an only intramuscular administration of g 0.50 in Procain-Pectine 2 %.

agar at 47 C. (agar 15 g, peptone 6 g, beef extract 3 g, water ad 1,000 ml) are poured on every plate. Holes of 6 mm are punched in the cold agar and in each one 2 drops of the fluid to be tested are placed (serum, blood or urine). The plates are incubated at 37 C. for exactly 24 hours. Accurate metric measurements of the inhibition halo calculating in the four directions the average between the edge of the hole and the lower limit of the inhibition zone are carried out. Controls were prepared which contained in different holes increasing quantities of antibiotics (DHSTRM or STRM) starting from 0.5 S. U. to 200 S. U.

Fig. I shows the result in mm (and the corresponding number of S. U.) of the inhibition halo produced by the serum of 6 patients suffering from pulmonary tuberculosis who were given a single intramuscular dose of 0.5 g DHSTRM (Pfizer) or STRM (Merck) diluted in pectine sol. at 2 % + procain 1 % in buffered saline solution at a PH of 7 (Eufarma-Florence, Italy).

Fig. 2 shows the result in mm (and the corresponding number of S. U.) of the inhibition halo produced by the blood of the same patients. For both tests specimens were taken at 4, 8, 12, 16, 20, and 24 hours after the intramuscular injection.

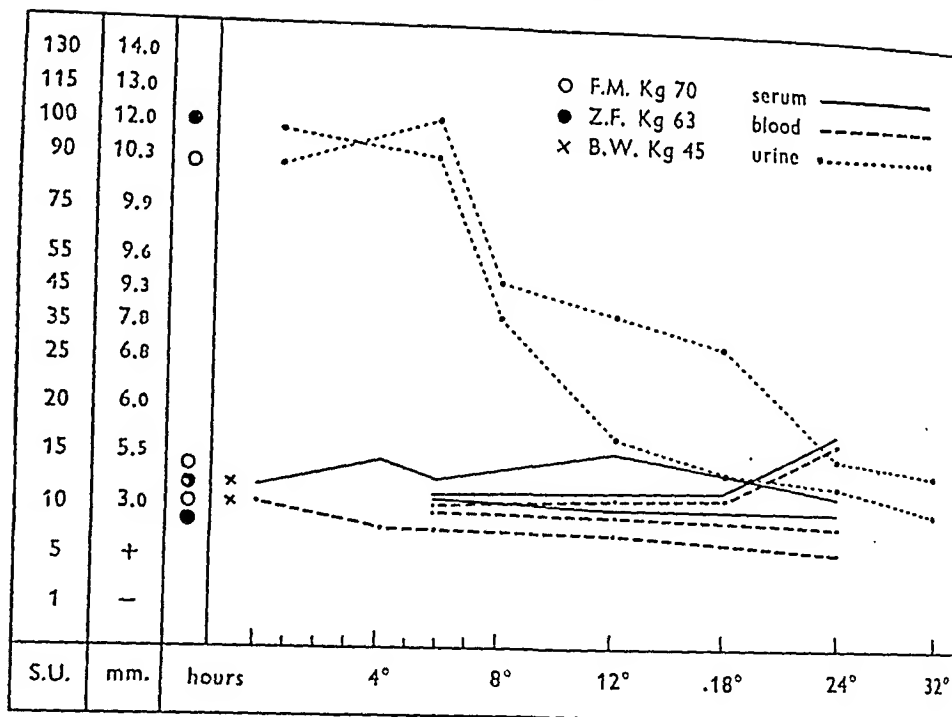


Fig. 3. Graphic of Dihydrostreptomycin in the serum, in whole blood and in the urine after only one intramuscular administration of g 0.25 in Procain-Pectine 2 %.

Fig. 3 shows in mm and in S. U. the inhibitory power of serum, blood and urine of 3 patients who were given a single intramuscular dose of DHSTRM in pectine sol. + procain (0.25 g). Two patients were healthy. In this test the antibiotic level was followed in the organic fluids at 6, 12, 18, 24 and 32 hours.

### Conclusions.

The intramuscular injection of 0.5 g Dihydrostreptomycin or Streptomycin diluted in 2 % pectine sol. + procain 1 % (buffered at PH 7) produces a concentration of the antibiotic in the serum corresponding in 50 % of cases to 17—96 S. U. (mg) per ml at the 24th hour.

When the antibiotic given is diluted in pectine sol. the sharp fall in the serum concentration in the 2nd and 3rd hour described by many investigators does not occur even when initial doses of antibiotic diluted in saline far bigger than those tested by us are used. The concentration of antibiotic in the serum in the various 24 hours specimens was much greater than that in the whole blood.

In the urine inhibition values corresponding to 6—8 S. U. at the 32nd hour are observed after a first intramuscular injection of 0.25 g in 2 % pectine sol. + 1 % procain. The inhibition values in the urine specimens examined in hourly fractions of the 24 hours are constantly far higher than those found in serum or blood.

The behaviour of the observed concentrations represented as a graph for every 4 hours for 24 hours follows in every way (contrary to what is usually accepted) a flat curve very similar to the curve observed in the test on the serum.

### Bibliography.

- (1) Hinshaw, H. C., Feldman, W. H., Carr, D. T., and Brown, H. A.: The clinical administration of dihydrostreptomycin in tuberculosis; a preliminary report, *Amer. Rev. Tuberc.*, 58, 523, 1948. — (2) Heilman, D. H., Heilman, F. R., Hinshaw, H. C., Nichols, D. R., and Rhoads, J. E.: Streptomycin; absorption, diffusion, excretion and toxicity, *Amer. J. Med. Sci.*, 210, 575, 1945. — (3) Ziniel, H. A., Flippen, H. F., Nichols, A. C., Wiley, M. M., and Rhoads, J. E.: Studies on streptomycin in man; I. Absorption, distribution, excretion and toxicity, *Amer. J. Med. Sci.*, 210, 421, 1945. — (4) Anderson, D. G., and Jewell, M.: Absorption, excretion and toxicity of streptomycin in man, *New Engl. J. Med.*, 233, 485, 1945. — (5) Hobson, L. B., Tompsett, R., Muschenheim, C., and McDermott, W.: A laboratory and clinical investigation of dihydrostreptomycin, *Amer. Rev. Tuberc.*, 58, 501, 1948. — (6) Feldman, W. H., Karlson, A. G., and Hinshaw, H. C.: Dihydrostreptomycin; its effect on experimental tuberculosis, *Amer. Rev. Tuberc.*, 58, 494, 1948. — (7) Edison, A. O., Frost, B. M., Graessle, O. E., Hawkins, J. E., Kuna, S., Mushett, C. W., Silber, R. H., and Solotorovsky, M.: An experimental evaluation of dihydrostreptomycin, *Amer. Rev. Tuberc.*, 58, 487, 1948. — (8) Waksman, S. A., Reilly, H. C., and Schatz, A.: Strain resistance of bacteria to antibiotic substances especially to streptomycin, *Proc. Nat. Acad. Sci.*, 31, 157, 1945. — (9) Rake, G., Pansy, F. E., Jambor, P., and Donovan, R.: Further studies on the dihydrostreptomycin, *Amer. Rev. Tuberc.*, 58, 478, 1949. — (10) Canada, R. O.: Streptomycin therapy in progressive pulmonary tuberculosis, *Amer. Rev. Tuberc.*, 56, 508, 1947. — (11) Levin, L., Carr, D. T., and Heilman, F. R.: Distribution of dihydrostreptomycin in various body fluids, *Amer. Rev. Tuberc.*, 58, 531, 1948.
-



From the Medical Clinic, Karolinska Sjukhuset, Stockholm.  
(Director: Professor Nanna Svartz.)

## Some Technical Points on the Measurement of Skin Temperature with Thermocouples.

By

ALVAR GJERTZ.

(Submitted for publication June 3, 1949.)

The ever increasing interest during the last few years in the disturbances in the peripheral arterial circulation, has resulted in the increased use of measurements of skin temperature, both as an aid in the diagnosis of these conditions and in the observation of the results of treatment. At the present thermometers based on the thermo-couple principle are used in measuring skin temperature, and many different makes of instruments are on the market. When correctly used, some of them give reliable values, while others, owing to their construction, give results which are impaired by an error, which may be large or small, and is often incalculable. It is proposed to present some of the technical aspects of this problem.

When thermocouples are used for the measurement of skin and other surface temperatures, it is the construction of the application junction and its mode of application which is primarily concerned in the magnitude of the error of measurement, and the constant junction and the recording instrument itself play a smaller part in this respect. Several authors have dealt with these sources of error and have attempted to indicate various ways of eliminating them as far as possible. The main problem is to arrive at an application junction which will assume the skin surface as nearly as possible without changing it. It must be emphasized that the reading on the recording instrument is only the difference in potential, and with it also the difference in temperature between the two junctions of the system, and nothing more. Therefore the method of measurement stands or falls with the possibilities of producing a temperature in the application junction which is as nearly as possible that of the skin surface.

The chief causes of the errors of measurement which can be ascribed to the application junction are as follows:



(Bailey, Bedford and Warner, Colburn and Hougen). The last-named authors pointed out that no covering of the junction and of the adjacent area should therefore be permitted, but in their experiments with skin-temperature measurements Bedford and Warner covered the junction and wires with strips of adhesive tape. They point out that the tape ensures good thermal contact between the couple and the skin and protects the junction from the cooling effect of the air, while it does not appear to interfere with the normal heat-loss from the skin. Sheard (1931) also drew attention to the fact that the junction or its mount must not be of such a nature or size that, if its temperature differs from that of the skin, it changes the latter owing to direct heat conduction, when applied to it.

### Calibration errors.

As Sheard (1944) pointed out, it is very important that the calibration of the application junction should take place under conditions comparable with those under which the couple is to be used later. Calibration is usually effected by dipping the junction and handle into a liquid, the temperature of which is varied and can easily be determined. It is a matter of course that, under such circumstances, the measurement errors previously mentioned, can be almost eliminated and a very even and constant calibration curve be obtained. On the other hand, in the case of a skin-temperature measurement which is effected by means of contact with the skin surface, these sources of error are present to a greater or less degree. The calibration curve therefore can hardly be considered to apply under these conditions. Only with the couples of very simple design which were described by Sheard (1944) and Lewis (quoted by Bedford and Warner) can the conditions when the immersion-calibration is effected and when the surface-temperature is measured be said to be something like comparable.

It should further be pointed out that the calibration of uninsulated junctions should not be effected in water but in some electrically insulating medium. The two metals may form a galvanic cell with water and the electromotive force may shift the calibration curve.

The requirements of an application junction can be summarized as follows:

- (1) The heat conduction through the wires to the junction must be reduced as much as possible. The wires should therefore be thin and so arranged that on both sides of the junction they can be brought into direct contact with the skin.
- (2) The surface of the junction should be small, so that the actual surface temperature is not changed owing to disturbed heat radiation or direct heat conduction from the junction.
- (3) The couple must be calibrated under such conditions that the calibration values are correct when the surface temperature is measured.
- (4) In order to make possible a number of successive measurements on different points, it should be possible to bring the junction to temperature equilibrium quickly after contact with the skin.

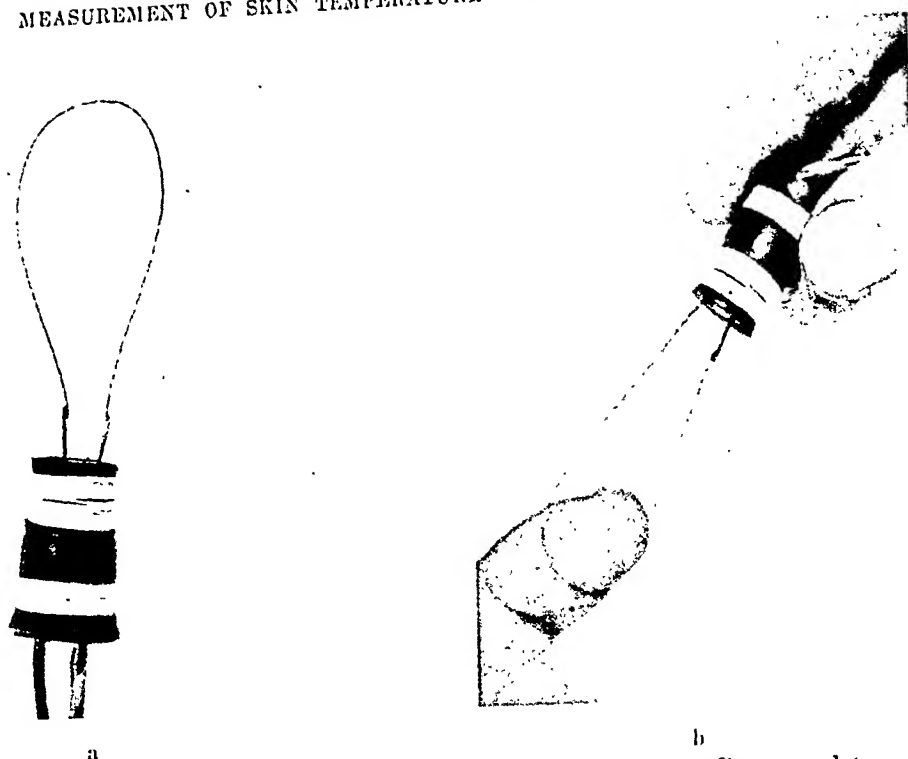


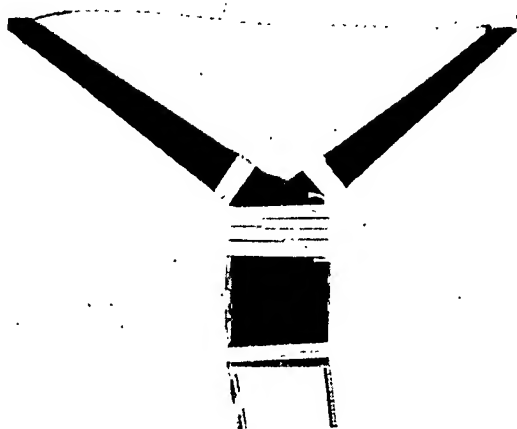
Fig. 1 a and b. Loop-shaped junction for temperature measurements on fingers and toes.

### Author's Investigations.

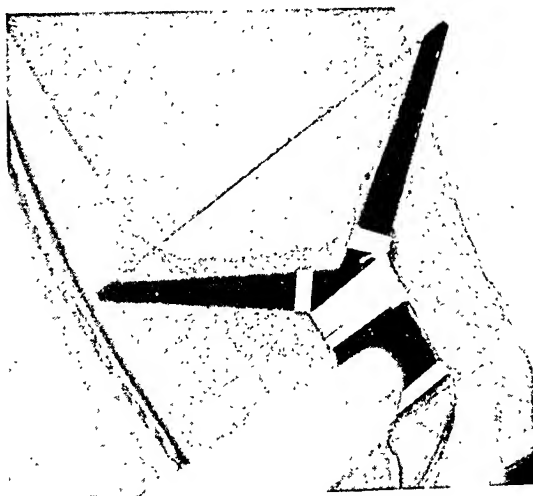
#### The construction of the application junction.

For several years application junctions of very simple design have been used in this laboratory for the measurement of skin temperatures. In principle they conform to the couples mentioned by Lewis and Sheard. These authors applied the junction and the nearest parts of the wires, to the skin area, the temperature of which was to be measured and fixed it all with a strip of adhesive tape. These junctions are intended for measurements for long periods of time and to remain in place during the whole experiment. When as is usual the temperature is measured at several points at the same time, the number of junctions and measurement points must be the same. In order to render possible measurements at different points with the same couple in rapid succession, the author mounted the wires of the couple in a handle, in such a way that the advantages of couples of this simple type were retained. For measuring the temperature of fingers and toes, the couple was given the form of a loop, and the 5—6 cm long terminal wires were fixed into a rubber handle (Fig. 1 a). For measurements on other parts of the body the wires were stretched between the prongs of a bakelite catapult-like fork, which at the same time serves as a handle (Fig. 2 a). With both this modifications the wires on both sides of the junction could be brought into satisfactory contact with the skin surface. With the loop type, contact between skin and wires was secured over an area corresponding to at least a quarter of the circumference of the finger, on both

sides of the junction (Fig. 1 b). With the fork type a 2—3 cm contact is effected on both sides of the junction (Fig. 2 b). Copper and constantan wiring consists of two wires 0.12 mm in diameter. The junction is formed by the soft-soldering of



a



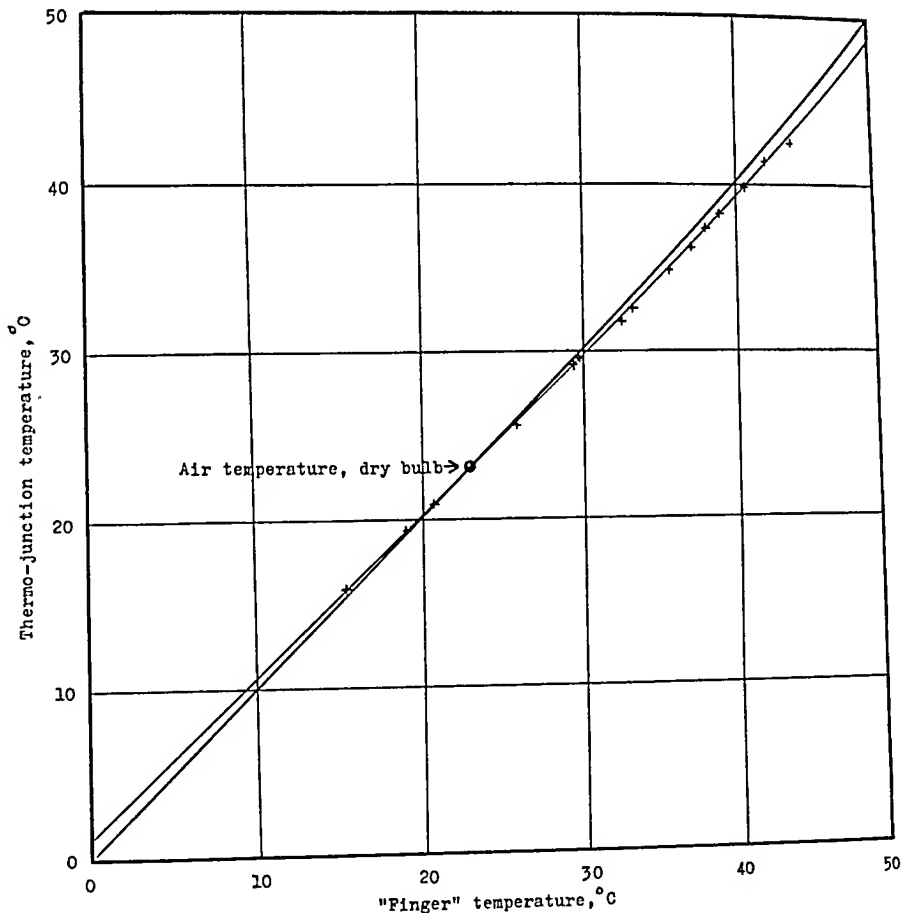
b

Fig. 2 a and b. Junction stretched between the prongs of a bakelite catapult-like fork.

wires side by side for a distance of 0.5—1 mm. The insulated constant junction was enclosed in a thermos flask full of water, the temperature of which could be read with an accuracy of  $0.1^{\circ}\text{C}$ .

When making measurements the recording instrument employed was mostly the galvanometer attached to Taylors »Dermatherm» (Taylor Instrument Companies, Rochester, N. Y.). The apparatus was calibrated by immersion of the junction and the terminal wires in liquid paraffin.





Graph 1. — "Finger" temperature.

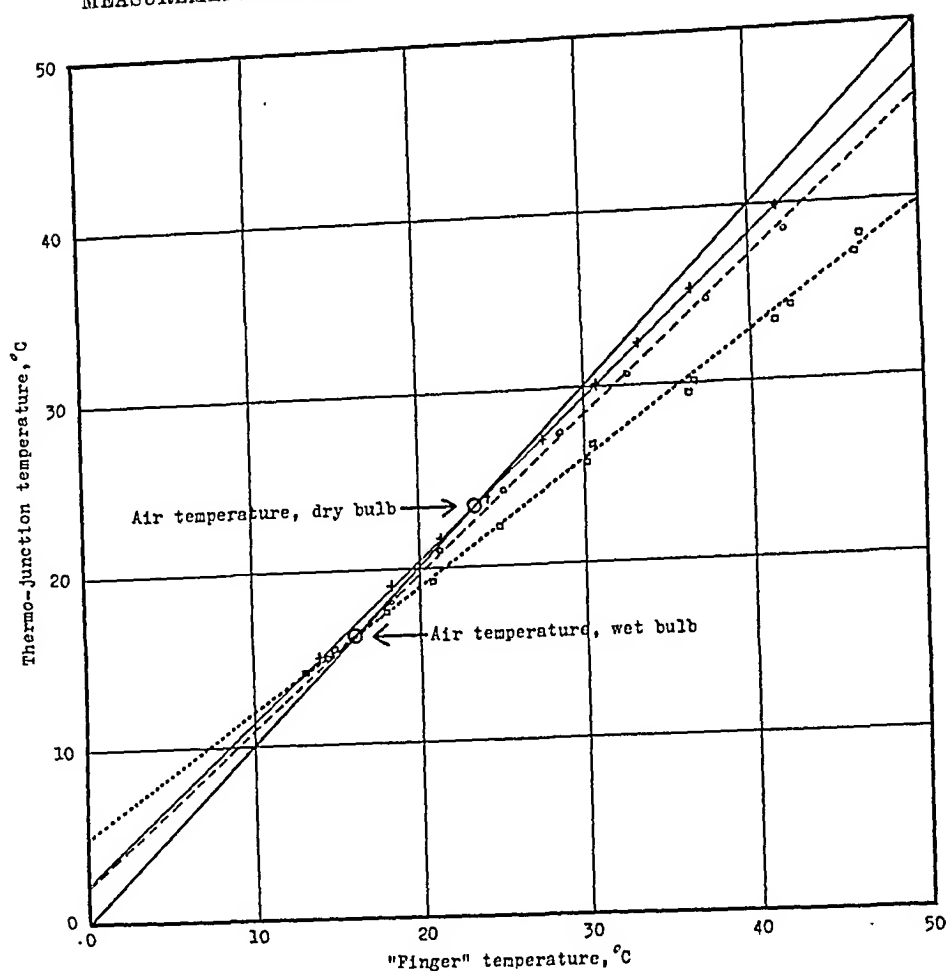
\* — \* Surface temperature recorded with thermo-couple.

Curve 1. Temperature measurement on a model surface. The temperature values recorded by means of the thermocouple show a systematic divergence from the surface temperature (= "finger, temperature") by about 5 % of the difference of surface temperature and air temperature.

This relatively inconsiderable and systematic difference between the recorded and the actual surface temperature values thus renders it possible to apply the calibration values established by immersion to surface temperature measurements also. As the heat properties in the rubber wall used in the model experiments probably do not differ materially from those of the skin, the observations made of the difference between the actual temperature and the recorded surface temperature hold good also in the case of skin surface measurements.

While therefore with dry surfaces there is relative constancy between actual and recorded surface temperature on the one hand and between surface temperature and air temperature on the other, conditions are different for temperature measurements on moist surfaces. The following experiment attempts to show this:

The experimental arrangement previously described was changed in such a way that the outer side of the rubber finger was covered with a thin layer of textile



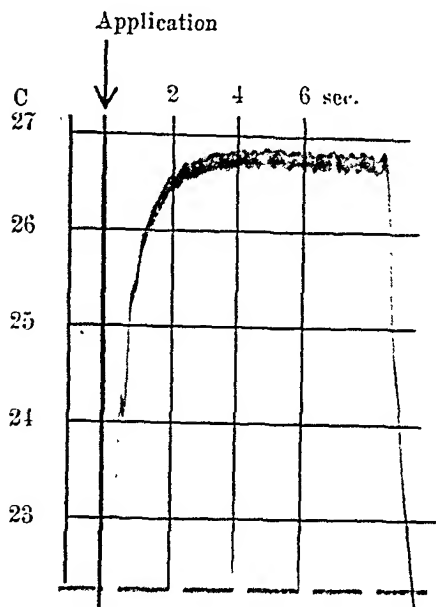
Graph 2. ————— "Finger" temperature.  
 —x—x— Surface temperature, clothed dry surface.  
 -o--o-- Surface temperature, clothed wet surface, air velocity  
 $\frac{1}{2}$  m/sec.  
 -o-----o-- Surface temperature, clothed wet surface, air velocity  
 2 m/sec.

Curve 2. Temperature measurement on a model surface. In the temperature measurement on a wet surface the systematic divergencies of the recorded values from the surface temperature are proportional to the difference of surface temperature and air temperature measured with a wet thermometer.

material. The junction of a loop-shaped element and the neighbouring parts of the wires were covered with a thin coat of insulating varnish with the object of preventing disturbing potentials if those parts became wet with water. Subsequently the temperature of the water in the rubber finger and on its clothed surface were recorded in the same way as in the preceding experiment. The surface temperature reading diverged somewhat more from the «finger temperature» than in the previous experiment because of a greater temperature gradient in the finger wall (rubber and material), but for the rest the curve of the recorded surface temperature was of the same type (Curve 2). After this the layer of textile material was damped with water and the experiment repeated. The recorded surface temperature values still



lie along a straight line, but it now intersects the »finger temperature» curve at a level which is considerably below that of the air temperature measured at the same time. In order to determine accurately the position of the point of intersection, the experiment was repeated with considerably stronger air circulation (2 m per sec.)



Graph 3. Adaptation time after application of the thermo-junction against a rubber surface.

Curve 3. Adaptation time to constant temperature in the case of application to a model surface about 4 sec.

than in the preceding experiment (0.5 m per sec.). This proved clearly that the curves intersected each other on a level with the temperature value of the wet air thermometer. In this case the »finger temperatures» is of course in no way representative of the actual surface temperature. The experiment was only intended to show that, in the case of temperature measurements on a damp surface, the systematic difference between the recorded and the actual surface temperature is proportional to the difference of surface temperature and wet bulb temperature and not to the difference of surface temperature and air temperature, as in the dry surfaces.

#### Adaptation rate.

Curve 3 shows the adaptation time, *i. e.* the time which elapses from the moment when the junction and its wires are applied to a surface, until a state of heat equilibrium

between surface, junction and surrounding air is reached. The same experimental arrangement was used as in the previous experiment (rubber surface), and a Moll's micro-galvanometer (Kipp and Zonen, Delft, Holland) was used as the recording instrument. It appears from the curve recorded that the temperature becomes constant already after about 4 sec.

#### Direct measurement of the mean temperature by multiple measuring points.

As Colburn and Hougen showed, it is possible with multiple application junctions to record directly the arithmetical mean for the temperature at two or more measurement points. These authors parallel-coupled two or more junctions and connected the latter to a common copper and constantan wire. The constant junction was simple. On immersion experiments with branch junctions at different temperatures they found that the values recorded with the thermocouples agreed largely with the arithmetical mean for the temperature of immersion fluids. However, in their arrangement it was necessary that the resistances in all the branch junctions should be exactly the same and this may present certain difficulties.

In our investigations the mean temperature for three different skin surfaces was arrived at as follows: Three thermocouples were connected in series, so that they formed a thermo-pile. Every second junction was constructed like the loop-shaped application junction previously described, the others serving as constant junctions. The thermo-pile was calibrated by means of the simultaneous immersion

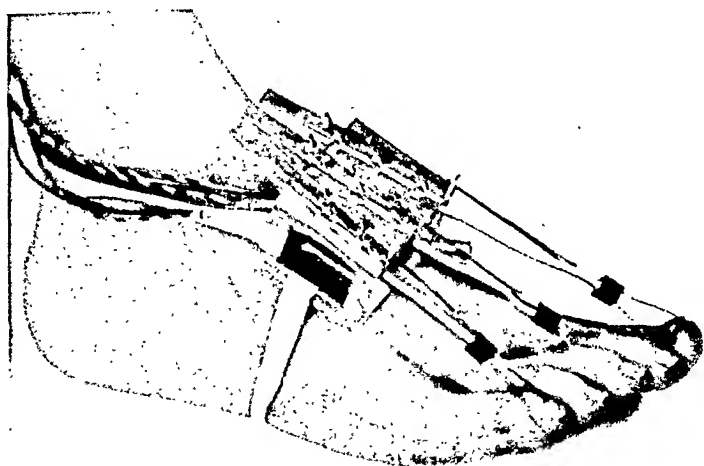


Fig. 3. Series coupled loop-shaped junction (thermopile) for direct determination of the mean temperature at several points.

of the three loops in a bath of liquid paraffin. The loops were then placed in separate paraffin baths at different temperatures, and the mean temperature recorded with the thermo-pile was compared with the arithmetical mean of the temperatures of the three paraffin baths.

Table I shows that there is satisfactory agreement between the mean readings and the arithmetical mean of the temperatures of the three paraffin baths. With this arrangement the distribution of the resistance within the different parts of the circuit is of no importance, as the deflections of the measuring instrument are determined by the resistance of the circuit only (which under these conditions must be considered constant), and the sum of the electromotive forces in the different junctions.

Table 1.

*A comparison between the arithmetical mean temperature in 3 different paraffin baths and the mean temperature recorded with a thermopile.*

Temp. of paraffin bath (°C) at the junction			Arithmetical means of the temperatures of the paraffin baths	Recorded mean value with thermocouples	Difference
I	II	III			
20.70	31.80	31.80	28.10	28.20	+ 0.10
31.05	20.70	20.70	24.15	24.10	- 0.05
20.75	30.10	20.75	23.85	23.85	± 0
35.40	28.20	20.95	28.20	28.30	+ 0.10
35.10	28.10	20.95	28.05	28.15	+ 0.10
27.60	33.25	21.00	27.30	27.25	- 0.05

This thermo-pile is well suited for measuring the skin temperature in such cases as for example vasodilatation tests. It can be built into an aluminium frame, which is fixed on the back of the foot with a loosely drawn strip of material so that the circulation is not impaired. The loops are placed round the toes, the temperature of which is to be measured, and are kept in position by small rubber bands, in such a way that the junctions and wires come into satisfactory contact with the skin surface, without exercising any considerable pressure (Fig. 3). A thermo-pile is placed on each foot, and with the help of a switch the thermo-pile of the right or left foot can be alternately coupled to the measuring instrument. This arrangement makes possible rapid and easy recordings of the mean temperature of the toes of each foot during the experiment.

### Summary.

In measurements of surface temperatures with thermocouples the construction of the application junction and the method of application are of decisive importance for the accuracy of the method. After a survey of various sources of error in this respect and of the possibilities of reducing them, a description is given of an application junction of simple construction intended for measuring skin temperatures. In principle the junction is of the same design as has been described earlier by Lewis and others.

In model experiments with temperature readings against a rubber surface, the recorded surface temperature values exhibit a systematic divergence from the actual surface temperature, in that more than 95 per cent of the difference between the surface temperature and the temperature of the surrounding air is recorded. In the measuring on moist surfaces the divergence is, however, relative to the difference between the surface temperature and the air temperature measured with wet thermometer.

In the application against a model surface, the junction has an adaptation time to constant temperature of about 4 sec. only.

The thermo-pile principle renders possible direct determinations of the mean temperature on two or more points. Experiments have shown satisfactory agreement between such determinations at three points and the arithmetical mean of the temperatures of the subjects of measurement.

It appears from the experimental results that the application junction described is satisfactory in exactitude and rapidity, and that the sources of error mentioned were much reduced. As the heat properties in the model surface employed in the experiments probably do not diverge materially from the corresponding properties of the skin, the observations made will probably also hold good for the measurement of the skin temperature.

### References.

- Aldrich, L. B.: A study of body radiation. *Smithsonian Misc. Coll.* 81, Nr 6, Publ. 2980, 1928. — Bailey, N. P.: The measurement of surface temperatures. Accuracies obtainable with thermocouples. *Mech. Eng.* 52: 553: 1932. — Bedford, T. and Warner, C. G.:

On methods of measuring skin temperature. *Journ. Hyg.* 34: 81: 1934. — Benedict, F. G., Coropatchinsky, V. and Finn, M. D.: Measurement of the skin temperature of humans. *Leopoldina (Amerikaband)* 4: 129: 1929. — Colburn, A. P. and Hougen, O. A.: Studies in heat transmission. I. Measurement of fluid and surface temperatures. *Ind. and Eng. Chem.* 22: 522: 1930. — Sheard, C.: The electromotive thermometer. An instrument and a method for measuring intramural, intravenous, superficial and cavity temperatures. *Am. J. Clin. Path.* 1: 209: 1931. — Sheard, C.: Temperature of skin and thermal regulation of the body. *Medical physics*. Ed. O. Glasser, The Year Book Publ. Chicago. Ill. 1523: 1944.

---

From the Medical Department III, Southern Hospital, Stockholm.  
(Acting chief: Eric Jonsson, M.D.)

## Endocrine Imbalance in Rheumatoid Arthritis and Rheumatoid Spondylitis: Hyperglycemia Unresponsiveness, Insulin Resistance, Increased Gluconeogenesis and Mesenchymal Tissue Degeneration.

Preliminary Report.

By

ROBERT LIEFMANN.<sup>1</sup>

(Submitted for publication June 15, 1949.)

Because of the occurrence of rheumatoid arthritis in association with certain endocrinopathies and because of the sex incidence (3:1 in women) the view was early held by this author that rheumatoid arthritis has an endocrine basis and should be investigated and treated from this point of view.

1. We find in rheumatoid arthritis not only inflammatory signs but also mesenchymal tissue degeneration: osteoporosis and generalized muscle wasting. Thus protein catabolism characterizes the disease.

2. Another finding is in carbohydrate metabolism. Changes in blood sugar regulation have been early reported (Pemberton and Foster 1920) but as yet unexplained. In a group of 25 female patients with classic type of slowly progressing rheumatoid arthritis and with typical X-ray changes, 20 or 75 % had a hyperglycemia unresponsiveness, when glucose tolerance tests were studied. In these tests, glucose is given orally, 1 gram per kilo and capillary blood sugar determined at half hour intervals. There was observed a delayed return to fasting level. Normally it is expected that blood sugar returns to normal and then subnormal within 2 hours. Here the blood sugar remained above 130 mg% at the end of 2½ hours or was abnormally elevated above 170 mg% at the one hour determination or later.

Five possibilities exist to account for this abnormality.

I) Anterior pituitary growth factor.

Cushing and Davidoff (1927) noted this type of blood sugar curve in acromegaly, and Houssay and Leloir (1935) demonstrated this to result independently from the adrenals. Long (1940) has further investigated this effect.

<sup>1</sup> 2314 South Road, Baltimore, Maryland, U. S. A.

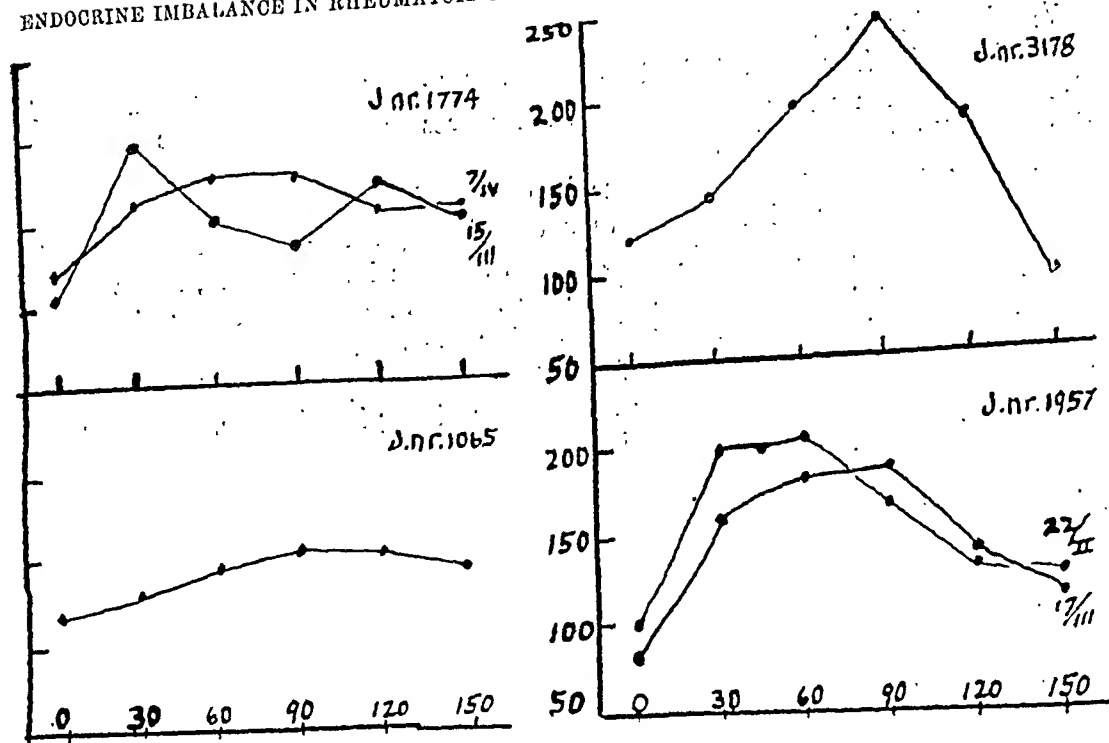


Fig. 1. Glucose tolerance curves in rheumatoid arthritis showing hyperglycemia unresponsiveness.

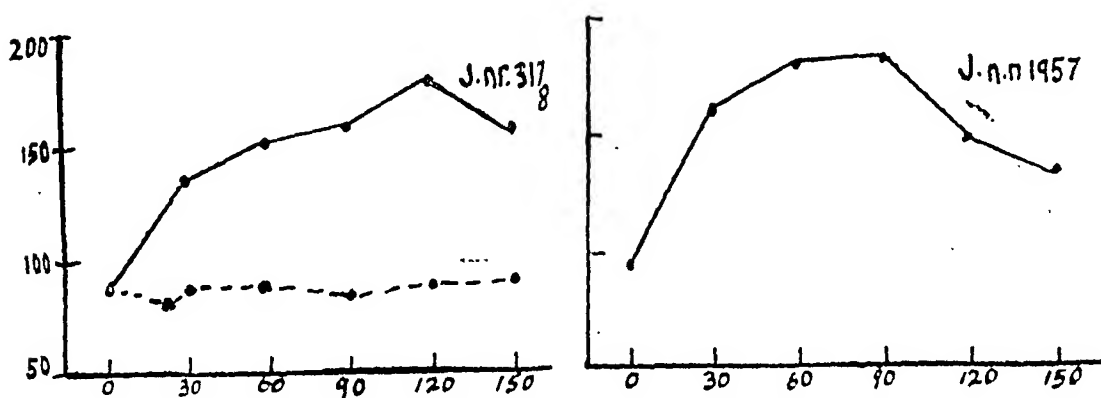


Fig. 2. Combined glucose-insulin tolerance curves in rheumatoid arthritis.  
Showing insulin resistance.  
(normal = dotted line)

## II) Adrenocortical sugar regulating hormones.

Cushing (1932) described this type of curve in hyperadrenocorticism (he thought the anterior pituitary basophilism the primary cause but Bauer later (1936) attributed the syndrome to the adrenals).

## III) Thyroid.

Geyelin (1915), Hamman and Hirschman (1917), and Holsti (1927) showed this type glucose tolerance curve to result when there is excessive thyroid secretion.

## IV) Insulin.

These blood sugar curves are seen in hypoinsulinism as is well known.

### V) Liver function.

Soskin (1943) has stressed the importance of liver disease in the production of abnormal blood sugar curves. However, the curves produced are not as markedly altered in liver dysfunction.

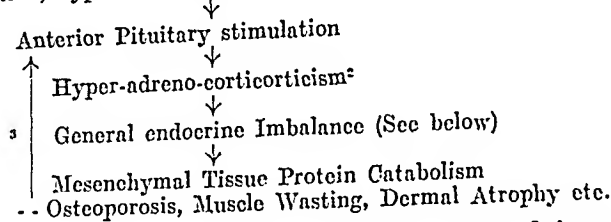
To further investigate this change in carbohydrate metabolism, insulin was given simultaneously with glucose in a combined glucose-insulin tolerance test (Himsworth 1939). A tenth of a unit insulin is given intravenously, and a tenth of a gram per kilo glucose orally. Normally there is no marked change from the fasting blood sugar value at any time during the test. However, in 4 cases of typical rheumatoid arthritis it was found that the abnormal curves in the glucose tolerance test were not appreciably affected by giving insulin, *i. e.* there was an insulin resistance (Fig. 2). Thus it is unlikely that a lack of insulin exists in rheumatoid arthritis to account for the hyperglycemia unresponsiveness (decreased tolerance to glucose).

### Insulin Resistance and Hypersecretion of Adrenal Sugar Regulation Hormones.

This type of insulin resistance found in rheumatoid arthritis patients has been described in hyperadrenocorticism (Frazer, Albright and Smith 1941). Insulin resistance has also been described in acromegaly (Davidoff and Cushing 1927) but the growth hormone is unlikely to be excessive in rheumatoid arthritis since there are no pathologic findings indicative of this condition. The adrenal sugar regulating hormones — 11-oxycorticosteroids (11-OCS) are involved in the reaction reported to precipitate the onset of rheumatoid arthritis — infection, and exposure etc. — «alarm reaction» — Selye 1937, — and have been measured in excessive amounts following these stimuli (Weil and Browne 1939, 1940, Venning and Browne 1947). 11-OCS hypersecretion can also account for the mesenchymal degeneration in rheumatoid arthritis — generalized osteoporosis, muscle wasting etc. similar to its effect in Cushing's syndrome (Albright and others 1941). 11-OCS has been demonstrated to stop the growth of bone and cartilage and cause degenerative changes (Baker and Ingle 1948). It can cause lymphopenia and possibly antibody changes (seen in rheumatoid arthritis) — Dougherty and White 1944. A proposed mechanism to account for 1) the precipitation of rheumatoid arthritis by infection, 2) mesenchymal tissue protein degeneration, 3) altered carbohydrate metabolism, is a shift of protein to sugar, *i. e.* an accelerated gluconeogenesis caused by a relatively excessive 11-OCS with a general hormone imbalance. Anterior pituitary, adrenocortical, and thyroid hormones predominate over testosterone-like, estrogen and insulin. The former three hormones when excessive are osteoporotic, protein catabolic, glucogenic. The latter three hormones oppose this action and are osteogenic, protein anabolic, and antiglucogenic. This is best represented diagrammatically as follows (Figs. 3 & 4).

This mechanism in rheumatoid arthritis can explain the successful treatment of the disease by such multifarious methods as 1) gold, artificial jaundice, etc. which are non-specific toxins, 2) various surgical procedures and physical therapy

Fig. 3. A proposed causal relation of some phenomena in rheumatoid arthritis.<sup>1</sup>  
Infection, hypersensitivity, cold, stress, trauma



<sup>1</sup> This also explains the duality of 1. precipitation and 2. treatment of rheumatoid arthritis by the same factor-injury. Injury is the first step in the diagram-, leading to step 2 and 3. Step 4 is not reached in the treatment (see footnote 2), but is in the precipitation of the disease (chronic hyper-adreno-corticicism → endocrine imbalance).

<sup>2</sup> There is some elevation of all the adreno-cortical hormones: ex. 17-ketosteroids rise to upper limits of normal, as well as estrogens etc. However there is a great elevation in the 11-OCS secretion to abnormally high levels (Forsham and others 1948).

<sup>3</sup> Note cycle set up: Anterior Pituitary → 11-OCS → Mesenchymal degeneration: ←

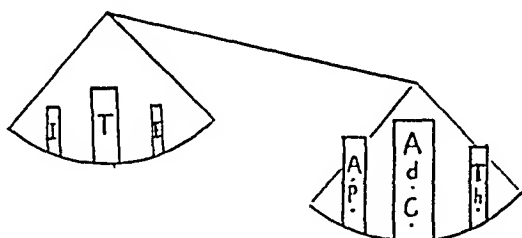


Fig. 4. A Chemical Balance: heavily weighted on the right.

Endocrine imbalance to account for the generalized mesenchymal degeneration in rheumatoid arthritis; showing anterior pituitary (A. P), adreno-cortical (Ad. C), thyroid (Th) = glucogenic, protein-catabolic, osteoporotic hormones when excessive — balanced against the testosterone-like (T), estrogen (E), and insulin (I) = anti-glucogenic, protein anabolic, osteogenic hormones.

— which are non-specific injuries, 3) foreign protein, vaccines, etc. — a type of injury (anaphylaxis). These procedures which may cause remission in the disease, possibly have the mechanism described in the above diagram. These same general stimuli are also thought to be precipitating factors in rheumatoid arthritis. When this mechanism is pathologically *prolonged* the result is the mesenchymal degeneration typical of the disease. Thus the paradoxical phenomenon of the precipitation of the disease and cure (remission) by the same factors is explainable.

It has been shown that testosterone will stimulate bone, cartilage, muscle and in general, mesenchymal tissue production. It has been shown also to inhibit anterior pituitary secretion and reduce adrenocortical 11-OCS (Mazer 1939, Selye 1940, Albright and others 1941, Venning and Browne 1947). Therefore, testosterone was administered to a series of rheumatoid arthritis patients and clinical and metabolic changes were studied during this treatment. Tentatively it was seen to be possible by testosterone treatment in a case of rheumatoid arthritis to normalize the abnormal glucose tolerance as well as eliminate insulin resistance in rheumatoid arthritis. However, 8—10 weeks are required for this effect (25 mg per 24 hours testosterone propionate intramuscularly). Positive nitrogen



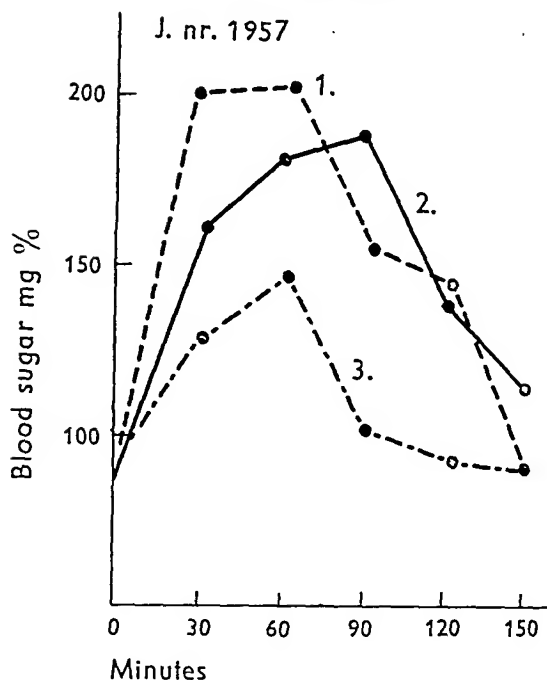


Fig. 5. Glucose tolerance tests during testosterone administration in a case of rheumatoid arthritis, showing normalization of glucose tolerance, following 7 weeks treatment with testosterone propionate (begun 22/ii)

1. = diabetic type curve 18/ii. Sedimentation Rate-50

2. = 17/iii Sed. Rate-25

3. = Essentially normal tolerance 12/iii. Sed. Rate-23

Case is a 51 yr.-old woman with a history of slowly progressing rheumatoid arthritis of the hands, wrists, and knees of 10 yrs. duration.

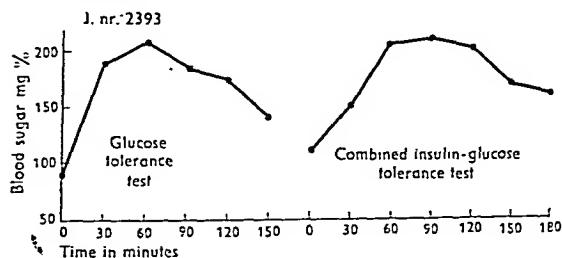


Fig. 6. Glucose tolerance test and combined glucose-insulin tolerance test in rheumatoid spondylitis showing hyperglycemia unresponsiveness and insulin resistance. This case, J. nr. 2393, is a 30-year-old male with typical rheumatoid spondylitis of seven years' duration involving the sacro-iliac joints and vertebral column, resulting in 'poker-back spines'. Left knee and right hip joints show rheumatoid changes.

balance occurred with weight gain. Joint function and condition of the musculature have been seen grossly to improve with treatment.

Further evidence of hypersecretion of adrenocortical hormones was seen in five consecutive male patients with rheumatoid spondylitis who had an abnormally elevated urinary 17-ketosteroid excretion. In one of these patients whose blood sugar regulation was followed the abnormal changes seen in rheumatoid arthritis were found — hyperglycemia unresponsiveness and insulin resistance. (Fig. 6.) Methyltestosterone administration was seen to reduce the 17-ketosteroid excretion

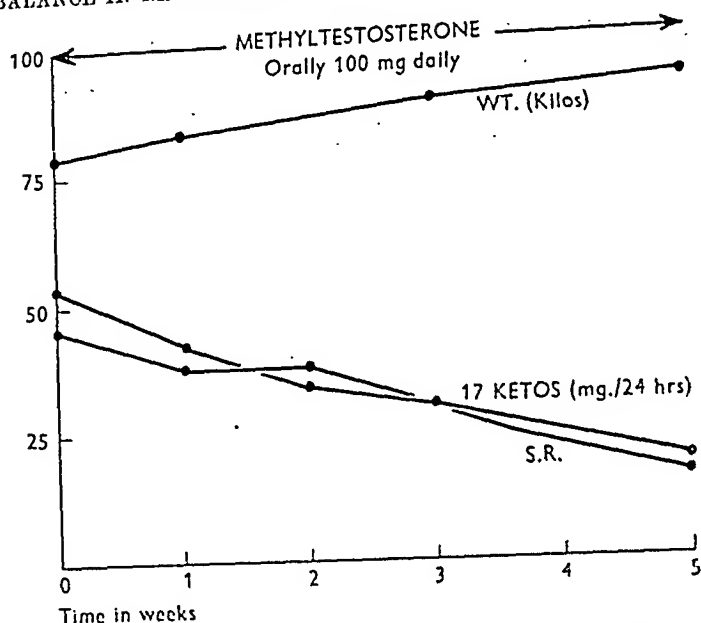


Fig. 7. Depression of 17-ketosteroid excretion with methyltestosterone administration in rheumatoid spondylitis (from 52 mg/24 hrs  $\rightarrow$  19 mg/24 hrs.). Simultaneous weight gain and decreased sedimentation rate were observed. J. nr. 2393.

to normal values (from 51 to 19 mg/24 hours) as well as reduce the sedimentation rate (from 45 to 18 mm). (Fig. 7.)

These findings in rheumatoid arthritis and rheumatoid spondylitis are subjected to statistical analysis in a future report.

### Summary.

Hyperglycemia unresponsiveness, insulin resistance, increased gluconeogenesis and negative nitrogen balance were found in rheumatoid arthritis and were explained on the basis of endocrine imbalance with a hypersecretion of adrenal sugar regulating hormones (11-OCS). The incidence of the disease, precipitating factors, and endocrine function in muscle and bone physiology support such a basis. This hormone imbalance with a shift of protein to sugar (accelerated gluconeogenesis) can explain the general mesenchymal degeneration in rheumatoid arthritis (osteoporosis, muscle wasting etc.). The hypothesis of endocrine dysfunction in the pathogenesis of rheumatoid arthritis was further investigated by means of hormone excretion studies as well as hormone administration. The above findings (in sugar and protein regulation) were also present in rheumatoid spondylitis as well as an additional finding — elevation in 17-ketosteroid excretion. Endocrine imbalance resulting from a pathologic defense mechanism and involving hyper-adreno-corticism explains the dual phenomenon of both the precipitation of rheumatoid arthritis as well as the «cure» (remission) by a large variety of injurious agents (toxemias, fever, surgical procedures, gold etc.). Sustained testosterone administration was shown to be capable of normalizing the «diabetic» glucose tolerance curves and eliminating insulin resistance in rheu-

matoid arthritis, as well as reduce the abnormally elevated 17-ketosteroid excretion in rheumatoid spondylitis. Stimulation of mesenchymal tissues resulted, as well as measurably improved joint function. The proposed mechanism is a correction of the hormone imbalance and reversal of the abnormally accelerated gluconeogenesis.

(This paper was prepared as above in 1947 with subsequent addition of new cases and references.)

### References.

- Albright, F., Parson, W., and Bloomberg, E.: *J. Clin. Endocrinol.* 1, 375, 1941. — Bauer, J.: *Schweiz. Med. Wchschr.* 39, 938, 1936. — Cushing, H.: *Bull. Johns Hop. Hosp.* 50, 137, 1932. — Cushing, H. and Davidoff, L. M.: *Arch. Int. Med.* 39, 674, 1927. — Davidoff, L. M. and Cushing, H.: *Arch. Int. Med.* 39, 751, 1927. — Dougherty, T. F. and White, A.: *Endocrinology* 35, 1, 1944. — Forsham, P. H., Thorn, G. W., Garnet Prunty, F. T. and Hills, A. G.: *J. Clin. Endocrinol.* 8, 15, 1948. — Frazer, R., Albright, F. and Smith, P. H.: *J. Clin. Endocrinol.* 1, 297, 1941. — Geyelin, H. R., *Arch. Int. Med.* 16, 975, 1915. — Hamman, L. and Hirschman, I. I.: *Arch. Int. Med.* 20, 761, 1917. — Himsworth, H. P.: *Lancet* 2, 171, 1939. — Holsti, O.: *Acta Med. Scandinav.* 66, 461, 1927. — Mazer, M. and Mazer, C.: *Endocrinology* 24, 175, 1939. — Pemberton, R. and Foster, G. L.: *Arch. Int. Med.* 25, 231, 1920. — Selye, H.: *Endocrinology* 21, 169, 1937. — Selye, H.: *J. A. M. A.* 115, 2252, 1940. — Soskin, S.: *Clinics* 6, 1287, 1943. — Venning, E. H. and Browne, J. S. L.: *J. Clin. Endocrinol.* 7, 729, 1947. — Weil, P. G. and Browne, J. S. L.: *Proc. Am. Physiol. Soc.* 121, 652, 1939. — Weil, P. G. and Browne, J. S. L.: *J. Clin. Investigation* 19, 772, 1940.
-

From the Surgical Department, The Provincial and City Hospital, Hälsingborg, Sweden,  
(Head: Erik Brattström, M. D.)

## On the Need for More Far-Reaching Indications for Operation in Cases of Ventricular Ulceration.

By

STEN BRATTSTRÖM, Hälsingborg.

(Submitted for publication June 1, 1949.)

The internal medical treatment of ventricular ulceration and its results has recently attracted considerable interest in this country, as also in America. The critical scrutiny of the results reached appear to have led to claims for a more aggressive and more positive attitude towards surgical treatment even from among internists.

The causes of this changed attitude towards surgical therapy are, firstly, the considerable number of ulcer patients who are not definitely cured of their illness by conservative treatment, secondly, the continually improved results of surgical treatment with its ever decreasing operation mortality, usually less than 5 %, and thirdly, the decline in the frequency of relapses and later troubles which, when they appear, are for the most part responsive to treatment by vagotomy or, in the case of the so-called post-coenal syndrome, by medication. They seldom need to be so disabling for considerable periods as a relapsing ulcer.

There is, however, a further reason which justifies more active therapy, and that is the great difficulty in deciding whether one is in the presence of a benign or a malignant ulcer. Not nearly sufficient importance seems to have been attached to this point. This is regrettable, but in a way understandable, for owing to natural reasons the great importance of this problem does not appear from statistics based on series where necropsy or operation has not been performed.

With the object of throwing light on the serious importance of the question, the series of *cancer ventriculi* of the Surgical Department of the Provincial and City Hospital at Hälsingborg during the years 1938—1948 has been gone through. The series comprises 131 cases of *cancer ventriculi* which were admitted for operation. All but 2 underwent operations. One was not operated on because the



increases, do not constitute absolute proof of the benign nature of the lesion, as has been pointed out by several authors, *inter alios*, Hellmer (5) (Sweden). In our material, too, there is a case where a malignant ulceration of the size of a hazelnut disappeared roentgenologically after 1 month's treatment, but after another 5 weeks' control had reappeared and was the size of a peppercorn. The patient's operation had been delayed for 10 weeks. Further cases of misleading decreases in the size of the ulceration are to be found in our examined material.

It will probably be hardly too much to assert that in the presence of a ventricular ulceration, where the clinical and X-ray findings are not sufficient for a certain and definitive differential diagnosis, the doctor all too often allows the length of the gastric anamnesis to determine his attitude. The table below will illustrate that this is often calamitous:

22 cancer ventriculi cases primarily diagnosed as ulcer cases.

Age	Sex		No. of cases
	♂	♀	
20—29.....	1	1	2
30—39.....	2		2
40—49.....		5	5
50—59.....	2	6	8
60—69.....	2	2	4
70—79.....		1	1

Duration of gastric trouble	
Time	No. of cases
3 mos. ....	2
3 mos.—6 mos. ....	2
6 mos.—1 year ....	1
1 year—3 years ....	9
3 years—6 years ....	6
6 years—9 years ....	1
17 years ....	1

In view of the protracted morbid histories of a large number of the cases, one naturally asks oneself whether one is confronted by a primary, slowly growing cancer, or whether it is a matter of ulcers passing into cancers. In our 22 cases the histological examinations, which were all made at the pathological-anatomical institution at Lund, 5 (probably 6) cases resulted in the diagnosis *ulcus carcinomatousum*. In all these cases the reports from the histological examinations state expressly that within an otherwise typical chronic callosus ulcer clearly atypical infiltrating parts of a malignant character had been found, which were sometimes described as adenocarcinomatous and sometimes scirrhous. In one of these patients the duration of the gastric trouble was given as one year. In the other 4 it was given as between 3—6 years. In 3 of these 5 cases there are also X-ray reports between 2 and 6 years old of *ulcus* at the places where *cancer* is now found.

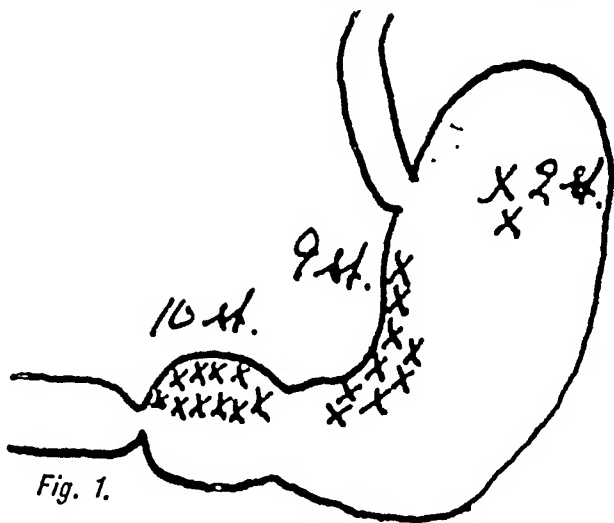


Fig. 1.

Note. In 1 case there was a cancer the size of a fist in canalis and one the size of a hen's egg at cardia. In 2 cases the cancer occupied such a large part of the ventricle that the primary localisation could not be established.

The localisations of the cancers in our cases appears from fig. 1 as far as they could be established with any degree of probability (which we considered was possible in 20 cases).

That in the case of the majority of our incorrectly judged and wrongly treated cases the ulceration was localized in the prepyloral part of the stomach is quite in conformity with the generally acknowledged differential diagnostic difficulties in that region, and the high frequency of both malignant and benign ulcers there. It will probably, however, not be an equally generally accepted conception that ulcerations in the angulus and along the *curvatura minor* involve almost equally great risks.

### Conclusions.

The general conception that the treatment of gastric ulcer is primarily a matter of internal medicine, and that surgical treatment should only be resorted to in the case of complications or an obstinately chronic course, must give place to a realisation that the differential diagnosis and treatment of gastric ulcer is primarily a surgical problem for the time being.

The mere fact that in an all too large percentage of cases (10—20 %) the diagnostic aids now available are not sufficient for the differential diagnosis as between malignant and benign ulcers to be made with an adequate degree of certainty, appears to me to warrant this statement.

Furthermore, the later results of the conservative treatment tend to prove worse than had previously been assumed, and both the immediate and the later results of surgical treatment appear to be steadily improving. Finally, the figures for the results in the case of the surgical treatment of cancer ventriculi, which have long been a sad story, ought to be able to be materially improved by following the principles of surgical treatment for gastric ulcers.

In the great number of cases where all the examination results unanimously indicate a benign lesion, conservative treatment should naturally be begun if other considerations indicate it. In this connection, however, the demand should be made that the treatment be given at a hospital or under the strictest control, so that the patient is not lost sight of. Further, a demand must be made for complete success in all respects of an adequately carried through treatment within one month and, what is equally important, monthly control by X-ray examinations for six months must show that the effect is lasting. In the case of an unsatisfactory result of the treatment or in the case of relapse, the case should be sent for operation without delay. Protracted and repeated treatments, and also long intervals between controls of 5—6 weeks, and even up to a couple of months, should not be allowed even if the practical consequences are inconvenient and burdensome.

### Summary.

The author points out that the critical scrutiny of the results of internal medical treatment in cases of ventricular ulcer seems to have led to a demand for a more

positive surgical attitude, even among internists both in Sweden and in America.

Various reasons are adduced for this, and the author specially emphasises that in all too many cases our present diagnostic possibilities do not permit of our making a definitive differential diagnosis as between malignant and benign ventricular ulcer with a sufficient degree of certainty. The statement is based on American and Swedish casuistics, and figures are given from material from the Hälsingborg Provincial and City Hospital for the 10-year period 1938—1948. Of 131 cases of cancer ventriculi admitted, all of which were operated on with the exception of 2, 22 proved to have been subjected to internal treatment on an average for 29.6 months before the operation under the diagnosis ventricular ulcer. Of the 2 cases which were not operated on, one was shown by X-ray examination to be inoperable; the other died of acute hemorrhage. The X-ray diagnosis was incorrect in 19 cases (14.5 %).

The all too long observation period during medical treatment, and the unreliability of the current criteria of the benign character of gastric ulcers are pointed out. A special warning is given against considering that a roentgenological decrease in or even the complete disappearance of the ulcer after treatment is a proof that the ulcer is benign. Examples are adduced of the total disappearance of ulcerations after treatment, although they were cancers. The histological examination indicated *ulcus carcinomatosum* in 5 (probably 6) cases out of the above-mentioned 22.

Finally, the author maintains that for the time being the differential diagnosis and treatment of gastric ulcer ought to be considered a surgical problem and adduces various reasons for this.

In the cases where it is considered that conservative treatment should be resorted to, the demand should be made that the treatment be given at a hospital or under the strictest control, so that the patient is not lost sight of. Further, the demand must be for the absolute success of an adequately carried out treatment within 1 month, and it is equally important that the effect should be lasting, as revealed by monthly X-ray control for 6 months. Protracted and repeated treatments and control intervals of 5—6 weeks up to a couple of months should not be allowed, even if the practical results of a change are burdensome.

#### References.

- 1) Allen & Welch: *Annals of Surgery* 1941, 114, 498. — 2) Marshall & Welch: *J. A. M. A.* 1948, 136, 748. — 3) Sandberg: *Svenska Läkartidningen* 1946, 25, 1633. — 4) Abramson: *Nord. Med.* 1948, 40, 2206. — 5) Hellmer: *Acta Radiolog.* 1946, XXVII, 153. — 6) Haraldsson: *Nord. Med.* 1948, 38, 778. — 7) Henschen: *Nord. Med.* 1949, 41, 439.



## Book Review.

F o l k e H e n s c h e n : Morgagni's Syndrome. 172 pages. Oliver & Boyd, Edinburgh and London 1949. Price: 30/- net.

In his first work on this subject, in 1936, Folke Henschen separated the triad hyperostosis frontalis interna, virilism, and obesity from the large and diffuse group of endocrine habitus anomalies. He proposed as a designation for that triad »Morgagni's Syndrome» after the man who was the first to observe it and, quite rightly, this name has become generally accepted.

As early as in 1936, and especially in his monograph in 1937, Henschen was able to present a comprehensive material collected from 1930, with a fundamental analysis of the delimitation, frequency, pathological anatomy, and genesis of the syndrome, which evidently had a very stimulating effect on further research work.

In the monograph under review Henschen collocates his earlier works with a considerable amount of his own material from more recent years, some of which has not been published previously.

The work is introduced with a meticulous survey of the literature from 1719 to 1947, in which Moore's roentgenological studies of 1935—36 of different forms of skull hypertrophy justly occupy considerable space. It is striking, if not surprising, how the literature in this field has increased tremendously after the epoch-making contributions from different points of departure of Moore and Henschen (1935—37).

Henschen's own material comprises autopsy cases of 1,000 women and 1,000 men, presented clearly and exhaustively in different groups of routine postmortem examinations and selected cases. — The author is undoubtedly right when he points out the advantage of an autopsy material in forming an objective picture of the syndrome.

Henschen has consistently insisted upon the frontal enostoses as the »leading symptom», chiefly because that symptom is very stable. Consequently the main part of the work is composed of a study of the morphology and morphogenesis of the enostoses, a part which is splendidly documented with 99 excellent reproductions of X-ray films, macro- and micro-photographs. This section concludes with a very convincing comparison and delimitation — which is important for the pathogenetic discussion — of the frontal hyperostoses and other forms of skull hyperplasias, especially puerperal osteophytes, hyperostosis calvariae diffusa (Moore), and hyperostosis frontoparietalis (Moore).





From St. Göran's Hospital, Stockholm.

## Age Distribution of Erythema Nodosum.

By

SVEN LÖFGREN.

(Submitted for publication June 22, 1949.)

---

The statements in the literature regarding the age distribution of erythema nodosum are extremely contradictory, a circumstance which to some extent is due to their being based largely on studies of hospital material which sometimes originated from children's wards and sometimes from wards for adults. They are also misleading for other reasons, which will be discussed in some detail further on.

A series of cases described by Levin in 1929 differs from those of other authors both in respect of its size and its composition. It comprised 1,621 cases, and consisted of the cases of erythema nodosum reported to the Health Centre of the City of Gothenburg by the medical health officers during the years 1908 to 1918, and as regards age distribution as well as other aspects it may be considered representative of the erythema nodosum material in Gothenburg during this period. Of the 1,621 cases, no less than 72.5 per cent were derived from ages below 16 years, and from this Levin concluded that erythema nodosum must be «a typical children's disease» (see fig. 3).

Two objections can, however, be raised against the methods used by both Levin and other investigators. In the first place, the difference between the sexes with respect to the incidence of erythema nodosum has not, for the most part, been taken into account, and in the second place, absolute figures have been stated for the occurrence of erythema nodosum and these have not been placed in relation to the size of corresponding age groups in the population. The disparity in the occurrence of erythema nodosum in the two sexes is otherwise well-known; it is mentioned by, among others, Levin, who asserts that «erythema nodosum among adults chiefly affects females, occurring fairly seldom among males. Among children also, girls show a slight preponderance, though the tendency is not so marked as it is among adults.»

Thanks to a statute from 1939, according to which physicians are obliged to report all cases of tuberculosis to the Tuberculosis Dispensaries, it is now possible to

gain a fairly good idea of the age distribution of erythema nodosum in Sweden. According to the directions issued by the State Board of Medicine in connection with this statute, »all forms of tuberculosis, including pleurisy, hilar adenitis and erythema nodosum», are to be reported. As to erythema nodosum, the statute is probably interpreted by many physicians, presumably by the majority, as necessitating the reporting of all cases to the dispensary, while by other physicians it is taken to apply only to cases where there is established or suspected active tuberculosis. The question as to the extent to which incomplete reporting of erythema nodosum cases might imply a selection, from the standpoint of the age distribution, will be discussed further on in this paper.

Preliminary results of this investigation, covering material from Stockholm for the years 1942—1944, have been described in an earlier publication (5).

### Material and Methods.

The main material used in this investigation consists of the erythema nodosum cases reported to the Central Dispensary of Stockholm during the years 1942—1944 and 1946—1947. (Information with regard to 1945 was not available.) For purposes of comparison corresponding information was also obtained from a tuberculosis dispensary serving a country district, viz. the Arvika Central Dispensary in the Province of Värmland. This district embraces a population of roughly 100,000 persons.<sup>1</sup>

The cases were classified into five or ten year classes and the incidence of erythema nodosum was then calculated in relation to the mean population in the respective age groups during the period in question.

### Results.

During the five years under discussion 1,282 cases of erythema nodosum were reported to the Central Dispensary of Stockholm, 211 of these being males and 1,071 females. Tables 1 and 2 show the total number of cases in the different age groups as well as the annual incidence of erythema nodosum per 10,000 inhabitants, calculated for the corresponding age groups in Stockholm. As the size of the population varies considerably in different age groups the relative frequency distribution of erythema nodosum cases deviates to a considerable extent from the distribution shown by the absolute figures. For both sexes, the distribution obtained is statistically significant when calculated by the  $\chi^2$ -method for heterogeneity (Bonnier & Tedin, p. 222), and in the majority of cases, as may be seen from the tables, there are significant differences, in respect of the incidence of erythema nodosum, between adjoining five or ten year classes. The age distribution is also

<sup>1</sup> I express here my thanks to Dr. Carl Gentz, head of the Central Dispensary of Stockholm, and to Dr. Rolf Lemming, head of the Arvika Sanatorium, who kindly placed the records on their erythema nodosum cases at my disposal. Thanks are also due to Dr. Anders Dalén, who assisted me in assembling information regarding the Stockholm cases.

Table 1.

Age distribution in 211 male cases of erythema nodosum in Stockholm for the years 1942—1947. Absolute figures and frequency per 10,000 inhabitants in different age groups. Distribution tested with the  $\chi^2$ -method for heterogeneity.

Age (in years)	No. of cases during 5 years	Mean no. of cases per year	Mean population	Annual no. of cases per 10,000 inhabitants	Differences in frequency of erythema nodosum between adjoining age groups
0—4.....	44	8.8	24,840	$3.54 \pm 0.53$	$3.33 \pm 1.09$
5—9.....	52	10.4	15,142	$6.87 \pm 0.95$	$1.06 \pm 1.35$
10—14.....	37	7.4	12,727	$5.81 \pm 0.96$	$2.09 \pm 1.17$
15—19.....	30	6.0	16,143	$3.72 \pm 0.68$	$1.51 \pm 0.80$
20—24.....	27	5.4	24,407	$2.21 \pm 0.43$	$1.52 \pm 0.48$
25—29.....	10	2.0	29,021	$0.69 \pm 0.22$	$0.55 \pm 0.24$
30—34.....	2	0.4	29,375	$0.14 \pm 0.10$	$0.23 \pm 0.19$
35—39.....	5	1.0	27,280	$0.37 \pm 0.16$	$0.20 \pm 0.20$
40—44.....	2	0.4	23,784	$0.17 \pm 0.12$	$0.07 \pm 0.16$
45—49.....	1	0.2	21,059	$0.10 \pm 0.10$	$0.04 \pm 0.12$
50—59.....	1	0.2	35,455	$0.06 \pm 0.06$	

$\chi^2$  for heterogeneity = 347.  $P < 0.001$  (10 degrees of freedom).

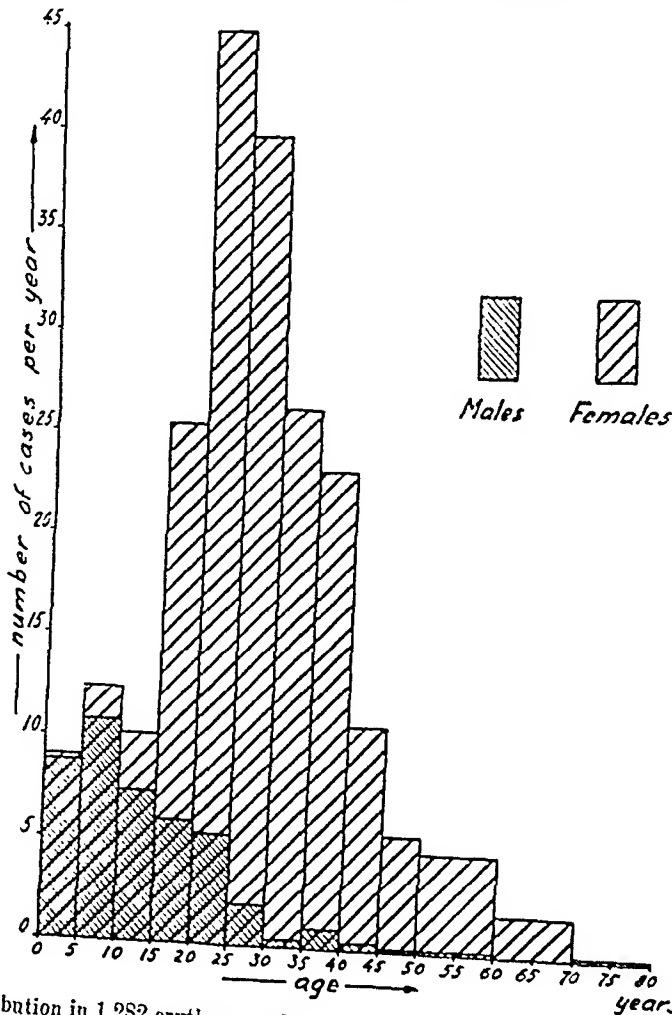


Fig. 1. Age distribution in 1,282 erythema nodosum cases in Stockholm 1942—1947. Absolute figures.

Table 2.

Age distribution in 1,071 female cases of erythema nodosum in Stockholm for the years 1942—1947. Absolute figures and frequency per 10,000 inhabitants in different age groups. Distribution tested with the  $\chi^2$ -method for heterogeneity.

Age (in years)	No. of cases during 5 years	Mean no. of cases per year	Mean population	Annual no. of cases per 10,000 inhabitants	Differences in frequency of erythema nodosum between adjoining age groups
0—4.....	45	9.0	23,626	$3.81 \pm 0.57$	$4.67 \pm 1.22$
5—9.....	62	12.4	14,629	$8.48 \pm 1.08$	$0.29 \pm 1.58$
10—14.....	51	10.2	12,449	$8.19 \pm 1.15$	$6.08 \pm 1.71$
15—19.....	127	25.4	17,799	$14.27 \pm 1.27$	$0.00 \pm 1.59$
20—24.....	224	44.8	31,393	$14.27 \pm 0.95$	$2.77 \pm 1.25$
25—29.....	198	39.6	34,428	$11.50 \pm 0.82$	$3.95 \pm 1.05$
30—34.....	131	26.2	34,717	$7.55 \pm 0.66$	$0.57 \pm 0.93$
35—39.....	116	23.2	33,261	$6.98 \pm 0.65$	$3.34 \pm 0.82$
40—44.....	54	10.8	29,639	$3.64 \pm 0.50$	$1.53 \pm 0.64$
45—49.....	28	5.6	26,571	$2.11 \pm 0.40$	$1.05 \pm 0.46$
50—59.....	24	4.8	45,236	$1.06 \pm 0.22$	$0.39 \pm 0.30$
60—69.....	10	2.0	30,033	$0.67 \pm 0.21$	$0.54 \pm 0.25$
70—79.....	1	0.2	15,029	$0.13 \pm 0.13$	

$\chi^2$  for heterogeneity = 636.  $P < 0.001$  (12 degrees of freedom).

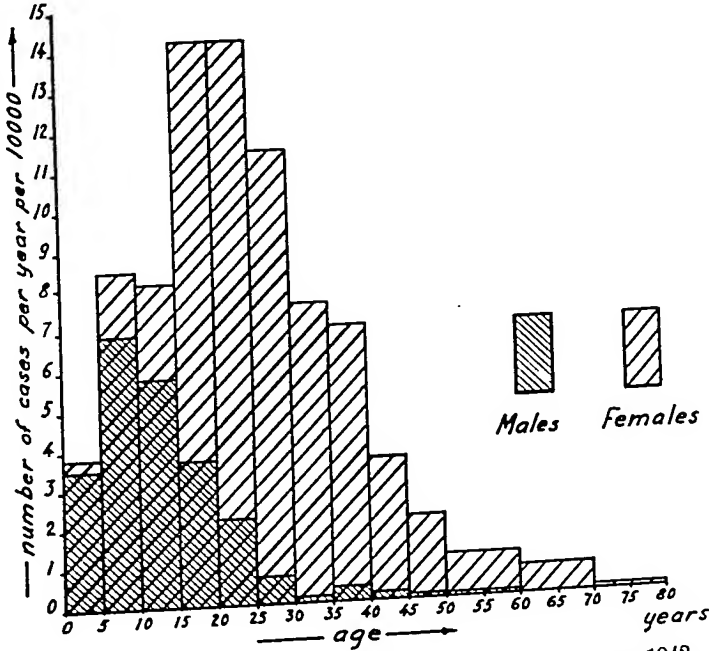


Fig. 2. Age distribution in 1,282 erythema nodosum cases in Stockholm 1942—1947. Frequency per 10,000 inhabitants in different age groups.

illustrated by charts showing the absolute number of cases (fig. 1) and the relative frequency for different ages (fig. 2).

It will be seen from the tables and diagrams that the frequency curve for the two sexes is approximately the same for the first fifteen years of life, the frequency

Table 3.

*Age distribution in 110 female cases of erythema nodosum from the Arvika Central Dispensary in Värmland for the years 1942—1946. Absolute figures and frequency per 10,000 inhabitants in different age groups.*

Age (in years)	No. of cases during 5 years	Mean no. of cases per year	Mean population	Annual no. of cases per 10,000 inhabitants
0—4.....	5	1.0	4,148	2.42
5—9.....	11	2.2	3,529	6.23
10—14.....	8	1.6	3,288	4.87
15—19.....	17	3.4	3,700	9.19
20—24.....	19	3.8	3,792	10.02
25—29.....	8	1.6	3,754	4.26
30—34.....	12	2.4	4,056	5.92
35—39.....	11	2.2	4,264	5.16
40—44.....	12	2.4	4,050	5.93
45—49.....	5	1.0	3,860	2.59
50—59.....	0	0.0	15,088	0.27
60—69.....	1	0.2		
70—79.....	0	0.0		
80—89.....	1	0.2		

being relatively low in the 0—4 age group and considerably higher in the 5—14 age group. The difference between the frequency figures for the 5—9 and 0—4 age groups is significant (for boys,  $3.33 \pm 1.09$ ; for girls,  $4.67 \pm 1.22$ ). Among the males, the incidence of erythema nodosum in general reaches its maximum just in the age-period 5—9 years.

The frequency figures are slightly lower for boys than for girls during the whole of the childhood period, but the difference is not statistically significant, either for any of the three five-year periods taken separately or for the entire fifteen-year period.

From puberty onwards, the curves diverge noticeably. The frequency drops rapidly among the males, the difference between the ages 10—14 years ( $5.81 \pm 0.96$ ) and 15—24 years ( $2.81 \pm 0.37$ ) being significant ( $3.00 \pm 1.03$ ). After 25 years of age erythema nodosum is just as uncommon in men as it is in women over the age of 60.

Among the females, the incidence of erythema nodosum shows a distinct increase after puberty, reaching its maximum in the 15—19 and 20—24 age groups. The difference in incidence, as compared with the 10—14 year period, is significant ( $6.08 \pm 1.71$ ). The incidence drops, admittedly, after the age of 25, but in the 25—29 year period it is still higher than in the 10—14 year period (the difference is statistically probable,  $3.31 \pm 1.41$ ). After 40 years of age it drops rapidly.

Summarizing, it may be said that, according to the evidence of this material, erythema nodosum occurs, in the male, most frequently between the ages of 5 and 9 years and is an uncommon occurrence after puberty, while in the female, it is commonest in the ten years following puberty.

For purposes of comparison, the results of an analysis of the series of erythema nodosum cases from the Arvika Central Dispensary are also reported here. A total of 129 cases of erythema nodosum, 19 males and 110 females, were reported to this dispensary during





Table 4.

*Etiologic distribution of erythema nodosum in different age groups (160 female patients). Relation between age and percentual proportion of cases of tuberculous and cases of streptococcal type tested with the  $\chi^2$ -method for heterogeneity. (Löfgren 1946.)*

Age (in years)	No. of cases	Etiologic type		
		Tuberculous type	Streptococcal type	Other types
15—24.....	64	50 (78.1 % $\pm$ 5.2)	3 (4.7 % $\pm$ 2.7)	11 (17.2 % $\pm$ 4.7)
25—34.....	63	35 (55.6 % $\pm$ 6.3)	9 (14.3 % $\pm$ 4.4)	19 (30.2 % $\pm$ 5.8)
35—44.....	33	10 (30.3 % $\pm$ 8.0)	14 (42.4 % $\pm$ 8.6)	9 (27.3 % $\pm$ 7.8)
		$\chi^2 = 21.2$ $P < 0.001$ (2 degrees of freedom)	$\chi^2 = 22.9$ $P < 0.001$ (2 degrees of freedom)	

relation to etiologic factors. In an earlier publication on the etiology and pathogenesis of erythema nodosum in adults it was, for instance, demonstrated that there was a significant relation between the age of the patients and the etiologic type of the disease (5). A comparison of the erythema nodosum cases in the 15—24, 25—34 and 35—44 age groups revealed that indications pointing to primary tuberculous infection in connection with erythema nodosum were present in 78.1 per cent of the cases in the first group, in 55.6 per cent in the second group and in only 30.3 per cent in the third group (table 4). Thus, the frequency of primary tuberculous infection in connection with erythema nodosum decreases with increasing age.

Because of the relation that has been found to exist between erythema nodosum and various etiologic factors it is not a priori improbable that the age distribution in this complaint may vary with time and place, according to the occurrence of infections that cause erythema nodosum. One must especially bear in mind the possibility that changes in the tuberculosis morbidity may have an influence on the frequency of erythema nodosum and thus on its age distribution also. From this point of view, it might be expected, for instance, that there would be differences in age distribution between an urban and a rural series of cases. The rural material used for comparison in this investigation showed, however, no appreciable divergence from the Stockholm material in this respect. Above all, it was found that in the rural series also, as in the urban material, the age of predilection for erythema nodosum in women was around 15 to 24 years.

The part played by the time factor in producing changes in the age distribution of erythema nodosum is, perhaps, of greater interest here. A comparison between the results of the present investigation and those obtained by Levin on the Gothenburg series from the years 1908—1918 may yield information on this aspect.

Levin's curve (fig. 3) as well as his statement that 72.5 per cent of his cases were below the age of 16 years would seem to indicate that erythema nodosum in Gothenburg between 1908 and 1918 was a typical children's disease. In my material of 1,282 cases of erythema nodosum, on the other hand, only 291, or 23 per cent, belonged to the 0—14 age group (fig. 1); if instead of using absolute figures we take

the relative frequency of erythema nodosum (fig. 2) the distribution in my material will be 35 per cent in the 0—14 age group. In both instances the figures give the impression that a strong displacement in the age distribution of erythema nodosum has taken place during the three decades that have elapsed between Levin's investigation and the present one.

To a certain extent, however, the difference is misleading, and for several reasons an adequate comparison between the two investigations is difficult to make. In the first place, Levin's study, as I mentioned further back, was based on a mixed series of men and women. In the second place, his classification into age groups is different from the system used in my material, and the exact distribution on dif-

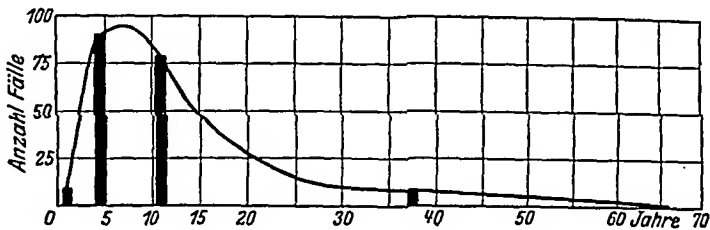


Fig. 3. Age distribution in 1,621 erythema nodosum cases in Gothenburg 1908—1918. (From Levin 1929.)

ferent age groups is not shown in his publication. Finally, he did not take into account in his investigation the size of the population in the different age groups.

From available statistics (6), however, it may be seen that the age distribution among the population of Gothenburg during the years 1910—1920 was quite different from what it now is in Stockholm. The population was relatively evenly distributed up to the age of 35 years, with variations from about 7,000 to 10,000 inhabitants of each sex in different five year classes. Levin's curve would thus not have been greatly affected if it had been based on relative frequency figures instead of on the absolute number of erythema nodosum cases. It would have had an entirely different appearance, on the other hand, if it had been divided up to apply to the two sexes. As the incidence of erythema nodosum, up to adolescence, was roughly the same for boys and girls in Levin's material also, an approximate frequency curve for the childhood years can be obtained for each sex by cutting the high peak for the 0—15 age period down to half. According to Levin's statement, that adult males seldom develop erythema nodosum, the frequency curve for the male sex in his material ought to have shown a steep drop towards the 0 level after puberty, and the females' frequency curve after puberty can thus be obtained by dropping Levin's curve slightly after the age of 15 years, to allow for the deduction of the relatively few male cases. Levin's conclusion, that erythema nodosum must be a *typical* children's disease, would thus, in his own material, seem to have been correct only with respect to the male sex. With regard to the female sex it is probable, admittedly, that the maximum incidence of erythema nodosum may have been between the ages of 5 and 15 years, but the preponderance over the following 5 year period cannot have been as great as the curve shown in figure 3 would indicate.

With the possibilities available for comparison it can thus be said that the age distribution of erythema nodosum in an urban material in Sweden is essentially the same now as it was thirty years ago, as far as the male sex is concerned, but that as regards the female sex the maximum incidence of the complaint has shifted from the years of childhood to the decade following puberty. As far as can be judged, this change seems to be connected with the decreasing incidence of tuberculosis and the consequent tendency towards a displacement of primary tuberculous infection away from childhood in the direction of the adult ages.

### Summary.

1. The age distribution of erythema nodosum has been studied in a material of 1,282 cases from Stockholm for the years 1942—1947; 211 of the cases were males and 1,071 females. The frequency of erythema nodosum in each sex was calculated per 10,000 inhabitants in different age classes.

2. The incidence of erythema nodosum was found to be roughly the same for both sexes between the ages of 0 and 14 years, with a slight preponderance in the case of the girls. From the age of 15 onwards the incidence drops rapidly among the males, their maximum being in the 5—9 age class. In the female sex, on the other hand, the frequency increases considerably after puberty, reaching the maximum in the ages of 15—19 and 20—24 years. The same age distribution was obtained in a rural material of 110 female cases of erythema nodosum.

3. The relation between age distribution and etiologic factors in erythema nodosum is discussed.

4. A comparison with a Swedish investigation from the years 1908—1918 shows that the age distribution among males is in essentials unchanged but that among females the maximum incidence of erythema nodosum has moved away from childhood to the ten-year period following puberty. This change is considered to be connected with the decreasing incidence of tuberculosis and the consequent displacement of primary tuberculous infection from childhood years to adult ages.

The costs of this investigation were defrayed by a grant from the Swedish National Association against Tuberculosis.

### References.

1. *Annuaire statistique de la Suède* 1948. — 2. *Annuaire statistique de la ville de Stockholm* 1943—1947. — 3. Bonnier, G. & Tedin, O.: *Biologisk variationsanalys*. Stockholm 1940. — 4. Levin, N.: Erythema nodosum in statistischer Beleuchtung. *Beitr. z. Klin. d. Tuberk.* 72, 1929: 641. — 5. Löfgren, S.: Erythema nodosum. Studies on etiology and pathogenesis in 185 adult cases. *Acta med. Scandinav.* 124, 1946: Suppl. 174. — 6. *Sveriges officiella statistik*. Folkräkningen 1910, II; 1920, III.

Department of Biochemistry, Marquette University School of Medicine, Milwaukee, USA.  
(Director: Armand J. Quick, M. D., Ph. D.)

## Studies on the Rôle of Calcium in the Coagulation of Blood.

By

MARIO STEFANINI,<sup>1</sup> M. D., M. Sc.<sup>2</sup>

(Submitted for publication May 2, 1949.)

---

### Introduction.

Considerable attention has been given in the past to the rôle of calcium in the process of clotting of blood. For a comprehensive review of the subject reference is made to the article by Ferguson (5). New techniques have recently permitted a new approach to the problem. The present paper will discuss the results obtained with these techniques and their bearing on the problem of the mechanism and nature of the reaction of calcium and related cations in the coagulation of blood *in vivo* and *in vitro*.

### Techniques Employed in the Course of the Present Study.

#### (1) *The use of Silicone in prevention of clotting of blood.*

Jaques and others (10) have shown that blood drawn by clean venipuncture using syringes, needles and glassware coated with a film of Silicone (methylchlorosylone, General Electric Dri-Film 9987) remains incoagulable for several hours or days without any marked modification of its physical, chemical or physico-chemical properties. The film markedly delays clotting by preventing the disintegration of platelets. As the lysis of platelets apparently supplies a factor of enzymatic nature which catalyzes the activation of an inactive plasmatic precursor to thromboplastin (22, 25, 28), it is obvious that the beginning of coagulation is correspondingly delayed. The technique is of invaluable help in the study of several problems of the coagulation of blood.

---

<sup>1</sup> New England Center Hospital, 30 Bennet Str., Boston 11. Mass. U. S. A.

<sup>2</sup> Senior Research Fellow, National Institute of Health, United States Public Health Service.

In coating glassware with Silicone, the agent is poured into the tube or syringe and the excess is allowed to drain. The glassware is afterwards repeatedly rinsed with distilled water and air dried. When needles are to be coated, Silicone is passed through them and the excess is removed by washing with a weak solution of ammonium hydroxide first and then with distilled water. In collecting blood great attention should be taken to avoid contamination with tissue juice or tissular thromboplastin as both conditions will determine the beginning of coagulation.

(2) *Decalcification of blood with Amberlite IR-100.*

Amberlite IR-100<sup>1</sup> is a phenolformaldehyde resin, which, when in the sodium cycle, removes calcium from blood completely by virtue of its ion exchange properties. The removal of calcium is best achieved in the quantitative relation of 1 gram of resin for 2.2 milliequivalents of blood calcium. This property of the resin was first utilized by Steinberg (42) to prepare blood for transfusion purposes. With this technique physical, chemical and physico-chemical properties of the blood are practically unaffected (42, 38).

As many samples contain impurities often responsible for inaccurate results, the purification of the resin becomes necessary for most of the specimens before they are used. A technique for this purpose has been described previously (38).

Twenty grams of Amberlite are covered with 100 cc of sulfuric acid 5 % by volume and the mixture is blended and stirred vigorously for five minutes. The resin is then washed with distilled water by decantation until the wash water is no longer acid. The material is treated with 100 ml of 5 % sodium carbonate volume, heated to approximately 70° C. and thoroughly stirred. The deeply colored supernatant fluid is then poured off and the process repeated until only little coloring matter can be extracted. The resin is finally washed with warm distilled water until all traces of sodium carbonate have been removed.

After purification has been completed, Amberlite is then prepared in the sodium cycle by adding to it 250 ml of a 5 % sodium chloride solution, stirring vigorously for thirty minutes and allowing to stand for sixty more minutes. The resin is washed with distilled water and filtered by suction until the wash water no longer contains chloride ions. The solid is finally dried in oven at 37° C. Three grams of the resin (amount sufficient to decalcify completely 10 ml of blood) are put in a tube approximately 1 per 15 cm (Figure 1). The lower extremity of the tube is closed by a plug of glass wool; the upper end by a cork covered with collodion, through which a No. 16 Silicone-coated needle is passed. Blood collected with minimum trauma by means of syringe and needle coated with Silicone is immediately passed through this column and collected in a test tube coated with Silicone. It is then repassed twice through the same column of Amberlite to assure complete decalcification.

Immediately after use the resin is washed free of all traces of blood with distilled water, then treated with 5 % sodium carbonate and recharged with sodium chloride. This procedure can be repeated several times without loss of activity of the Amberlite.

Blood which has been treated with Amberlite IR-100 fails to clot after addition of thromboplastin and contains, if any, amounts of calcium which cannot be detected by analytical methods. Number of red blood cells, white blood cells, platelets and percentage of hemoglobin, hematocrit value and specific gravity are moderately increased due to slight hemoconcentration. Values of blood sugar, urea nitrogen, uric acid, total protein, albumin/globulin ratio, non-protein nitrogen,

<sup>1</sup> Amberlite IR-100 analytical grade is supplied by the Resinous Products & Co., Philadelphia, Pennsylvania, U. S. A.

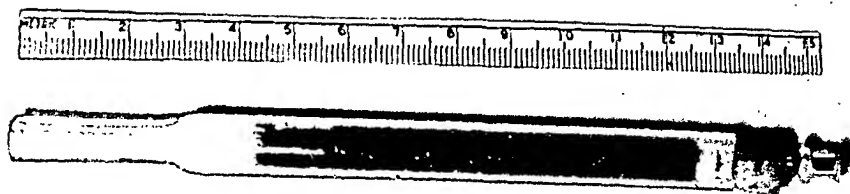


Figure 1. The tube employed for decalcifying blood with Amberlite.

(The tube, the plug of glass wool and the needle No. 16 are all coated with Silicone; the cork with collodion.)

(Courtesy of the Proceedings of the Society for Experimental Biology and Medicine.)

cholesterol, creatinine, inorganic phosphorus do not show any substantial changes. Serological properties are also unaffected. Only the sedimentation rate of erythrocytes appears consistently decreased when compared to that of citrated or heparinized blood. Among the factors involved in the coagulation, prothrombin activity and concentration of the «labile factor» are unmodified. The fibrinogen level is slight decreased (10 to 15 per cent), but not enough to cause any substantial change in the coagulability of the blood. Antithrombin activity, determined with the method previously suggested (37), is equal to that of oxalated plasma and much higher than that of citrated plasma (reasons to explain this finding will be given later). Finally, on recalcification, the clotting time of Amberlite blood or plasma is considerably shortened, but a similar result was obtained with oxalated or citrated blood. Amberlite removes calcium from whole blood, plasma or serum completely. While the presence of heparin in the treated blood does not modify the decalcifying activity of the resin, that of sodium citrate interferes with the decalcification of blood, in direct proportion with the concentration of the anticoagulant (Table 1).

Table 1.

*The effect of varying amounts of sodium citrate on the decalcifying activity of Amberlite (Average of several determinations).*

Sodium citrate mM.	Calcium left in plasma (mg%) <sup>1</sup>
10	1.4
20	3.6
30	4.7

### (3) Preparation of stable native plasma. (26.)

Venous blood is collected by means of syringe chilled before use and needle coated with Silicone. The blood is immediately transferred to Silicone-coated tubes (immersed

<sup>1</sup> Sodium citrate was first added to blood collected by venipuncture. The blood was then passed through a column of Amberlite and the plasma level in calcium determined with the method of Clark and Collip (2).

in iced water) and covered with mineral oil, to prevent excessive escape of  $\text{CO}_2$ . The blood is then centrifuged at 4,000 r.p.m. for 15 minutes in an angle centrifuge. The plasma is finally transferred to a new Silicone-coated tube kept in ice, by means of a Silicone-coated pipette.

(4) *Preparation of the gel of tricalcium phosphate and of deprothrombinized plasma.*  
(26.)

One liter of calcium chloride solution containing 66.6 g of the anhydrous salt is added slowly with vigorous stirring to a solution of trisodium phosphate containing 158 g of the salt in one liter of distilled water. The pH is adjusted to 7. The precipitate of  $\text{Ca}_3(\text{PO}_4)_2$  is washed by decantation until all traces of sodium chloride are removed. The suspension is then made up to one liter and has therefore a concentration of 0.2 M. From this stock solution a preparation of 0.005 M is made by diluting 2.5 ml with 97.5 ml of distilled water. One ml of the diluted suspension is then transferred to a small test tube and centrifuged to pack the gel. The water is poured off, the tube drained and 1 ml of plasma added. The tricalcium phosphate and the plasma are thoroughly mixed and allowed to stand at room temperature for ten minutes. The absorbant is finally separated by centrifugation.

Oxalated plasma treated with the gel at the concentration of 0.005 M for human and of 0.006 M for dog and rabbit has lost completely its prothrombin activity. The concentration for optimal absorption may, however, vary in gels prepared at different times and has to be determined for every new batch. The gel removes about 1.6 % of the protein content of plasma; about 3 % of fibrinogen and a minimal amount of the «labile factor». The loss of prothrombin activity is due to the complete absorption of prothrombin.

### The Optimal Concentration of Calcium for Coagulation of Blood.

While studying the decalcifying activity of trisodium citrate, Sabbatani (31) noticed that the amount of calcium normally present in blood is larger than that required for optimum clotting. Vines (43), confirming this result, established that only 1/17 of the amount of calcium available in blood is necessary to restore clotting of oxalated plasma. Nordbö (17), after obtaining calcium-free blood by flushing it with 5 % saline solution on an ultrafilter (method which, like the Amberlite technique, permits the removal of calcium without addition of the usual anti-coagulants), determined that 0.6 mg% of ionized calcium are all that is necessary to initiate coagulation. Shortly later, Ransmeier and McLean (29) found  $0.35 \pm 0.001$  mM  $\text{Ca}^{++}$  to be the concentration necessary for clotting and 1.25 mM that necessary for optimal clotting of citrated human plasma. Shifting of the pH to the acid or alkaline side caused an increase of the amount of  $\text{Ca}^{++}$  required for clotting in either case.

The introduction of Amberlite has obviously permitted a more reliable study of this problem. Little attention has been given in the past to the fact that, if the lysis of platelets is not prevented when collecting blood, the process of coagulation will be well on its way when the anticoagulant is added. This can explain in part some of the controversial results presented in the literature. By using Silicone-coated glassware and taking precautions to prevent contamination of the blood with tissue



juice, blood can be obtained in which the lysis of platelets is almost completely prevented and that can be then completely decalcified with Amberlite without modification of its properties. By direct addition of known amounts of calcium salts to this blood it becomes therefore possible to determine the effect of calcium on the clotting of blood and plasma on a correct quantitative basis.

In our experiments blood was obtained by venipuncture, taking precautions to avoid injuring tissues and foaming. Needles, syringes and tubes in which blood was collected were all coated with Silicone and the blood immediately passed through Amberlite according to the technique described above. Tubes and syringes were chilled before use and the decalcified blood kept in ice until used.

To remove traces of calcium from the thromboplastin, sodium oxalate (0.1 ml of 0.1 Na oxalate per each rabbit brain) was added before triturating the brain with acetone. The solution of calcium chloride used in recalcification was made isotonic to blood (10.73  $\frac{g}{100}$ ) and then diluted to the concentration desired by mixing with physiological saline. 0.4 ml of blood or plasma, previously decalcified with Amberlite, were added to 0.1 ml of  $\text{CaCl}_2$  of the desired concentration and the clotting time of the mixture determined. Pyrex tubes with an internal diameter of 11 mm were used. All observations were carried out at 37° C.

The results presented in Table 2 show that the shortest coagulation time for human blood is obtained at a concentration of calcium chloride of approximately 1.5 mM, exactly the normal blood level of calcium. A minimum coagulation time is obtained, however, over a wide range of calcium concentrations. Below 1.5 and above 4 mM a progressively more marked delay in coagulation occurs. Coagulation

Table 2.

*Influence of the concentration of calcium on the coagulation time and the prothrombin time of human blood and plasma decalcified with Amberlite.*

Concentration of $\text{CaCl}_2$ mM	Coagulation Time <sup>1</sup> (in minutes)		Prothrombin Time (in seconds)
	Blood	Plasma	
0.2	> 60	> 60	
0.5	8 $\frac{3}{4}$	7 $\frac{1}{4}$	19
1	6	4 $\frac{1}{4}$	14.5
1.5	5 $\frac{3}{4}$	3 $\frac{3}{4}$	13.5
2	5 $\frac{3}{4}$	2 $\frac{1}{2}$	12
4	5 $\frac{1}{2}$	2	
5			12
6	6 $\frac{3}{4}$	2 $\frac{1}{2}$	
8	9	3	
10	9	3 $\frac{1}{2}$	12
12	10 $\frac{1}{4}$	5 $\frac{3}{4}$	
14	11	9	
16	11 $\frac{1}{2}$	9 $\frac{1}{4}$	
18	13 $\frac{1}{2}$	21	
20	14 $\frac{1}{2}$	38	13
30			13.5
40			15
50			16.5
60			18

<sup>1</sup> To four volumes of blood or plasma treated with Amberlite one volume of  $\text{CaCl}_2$  solution was added.

of plasma follows essentially the same pattern except that the clotting time is shorter. This can be explained, at least in part, by the fact that the clot can be detected earlier in plasma than in whole blood.

The Amberlite technique also permits determination of the amount of calcium necessary for the optimal conversion of prothrombin to thrombin in the presence of an excess of thromboplastin, a most controversial subject (20, 43, 19, 12). Again, Table No. 2 shows that, using the one-stage method for the determination of prothrombin, optimal prothrombin times are obtained with a wide range of concentrations of  $\text{CaCl}_2$  (from 2 to 10 mM). Higher or lower dilutions determine a delay in the clotting time of the mixture.

A few conclusions can be drawn from this group of experiments. First, that the amount of calcium required for optimal coagulation is approximately equal to the concentration normally found in blood. Clotting still occurs, however, in not greatly delayed time, with much lower concentrations of calcium especially if the amount of thromboplastin present is increased (which may easily occur if crude techniques are used). This explains why much lower figures have been given by previous workers (44, 34) as the level of calcium necessary for clotting. It may also be said at this point that the coagulation time, while very sensitive to changes of concentration of the available thromboplastin, is only minimally influenced by variations of the blood calcium level which may occur in physiological or pathological conditions. The only case so far described in literature in which a hemorrhagic condition with prolongation of the clotting time was associated with a decreased calcium blood level is that described by Snyder (33). On the other side, it has been repeatedly observed that patients with tetany and calcium level as low as 4.6 mg% showed no sensible modifications of their clotting time, and likewise dogs in whom blood calcium level had dropped to mg 4—8 % after parathyroidectomy still presented an almost normal clotting time (30). Likewise, no case is known in which hypercalcemia was accompanied by hypercoagulability. Dogs in whom, with the use of parathormone, calcium levels as high as mg 26—28 % were produced, showed no significant shortening of their clotting time (30). Finally, in a large series of cases of sprue with evident intestinal malabsorption and hypocalcemia of different grade but consistently normal prothrombin activity, no changes of blood coagulability were observed (35, 39).

### The Influence of Calcium on the Different Phases of the Process of Coagulation of Blood.

Recent work by Quick and associates in this Laboratory (22, 28) has presented strong evidence that the process of coagulation of blood is to be considered as a three-step reaction (Figure 2). In the first step, an enzymatic factor (thromboplastinogenase), liberated by the lysis of platelets, activates a plasmatic globulin (thromboplastinogen) to active thromboplastin. In the second step, the two components of the so-called prothrombin complex (27) react stoichiometrically with calcium and thromboplastin to form thrombin. During the third, thrombin acts

enzymatically on fibrinogen forming thrombin. For more complete details, reference is made to previously reported results (28).

It is well known that calcium is especially active in the second step of the process of coagulation (activation of prothrombin to thrombin), and evidence of the stoichiometric nature of this reaction has been previously submitted (24, 41). In this paper data will be presented to show the influence of the concentration of calcium on the phases of the clotting process leading to the activation of thromboplastin and to the formation of fibrin.

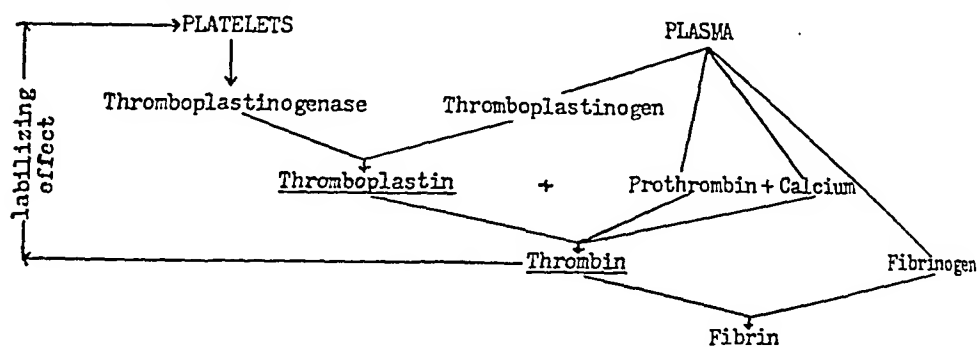


Figure 2. Factors and phases of the process of coagulation of blood. (Comment in the text.)

(1) *The influence of the concentration of calcium on the consumption of prothrombin.*

The full understanding of the rôle of thromboplastin in the coagulation of blood has always been handicapped by the lack of reliable assay methods. Quick has recently introduced a method, the prothrombin consumption test, which appears to indicate specifically defects in the activation of thromboplastin<sup>1</sup> and has supplied much useful information. The method (22, 40) consists in determining, through the recording of the prothrombin time of serum at variable intervals after the completion of clotting, the percentage of prothrombin consumed during the process of coagulation. In presence of a normal concentration of prothrombin and optimal level of calcium it is directly related to the concentration of active thromboplastin present in blood.

The technique for the determination of the prothrombin consumption is briefly summarized here. Two samples of blood or native plasma (2 ml each) are transferred to Pyrex tubes with an internal diameter of 11 mm kept in water bath at constant temperature of 37° C. and the clotting time recorded. Thirty and sixty minutes after the completion of clotting, respectively, one of the specimens is centrifuged for two minutes at 2,000 r.p.m. and the prothrombin time of serum is immediately determined with the following procedure: 0.1 mm of oxalated plasma deprothrombinized with tricalcium phosphate according to the technique described earlier; 0.1 ml of rabbit brain thromboplastin; 0.1 ml of 0.02 M  $\text{CaCl}_2$  and 0.1 ml of the serum under examination are rapidly added in a Pyrex test tube kept in water bath at 37° C. and the clotting time recorded.

By means of the Amberlite and Silicone techniques, it becomes possible to study quantitatively the effect of varying the concentration of calcium on the extent of

<sup>1</sup> This defect can be due to a deficiency of thromboplastinogen as in hemophilia (22), or of thromboplastinogenase as in thrombocytopenic purpura (28), or to the presence of a circulating anticoagulant with inhibitory activity on thromboplastinogenase (25).

the consumption of prothrombin. This can be done by obtaining native decalcified blood, cause its clotting with the addition of accurately measured quantities of  $\text{CaCl}_2$  to different samples and then determining the percentage of prothrombin consumed in each one at definite intervals of time after coagulation is completed.

In our experiments the following technique was followed: blood obtained by venipuncture with Silicone technique was decalcified with Amberlite and then centrifuged at 2,000 r.p.m. for five minutes. The supernatant plasma was collected in a Silicone-coated tube kept in ice. To 0.2 ml of solutions of calcium chloride of different concentration prepared in a series of tubes kept in water bath at  $37^\circ \text{C}$ . 0.5 ml of decalcified plasma were added and the clotting time of the mixture recorded. The prothrombin time of serum was determined one hour after the completion of coagulation according to the technique described.

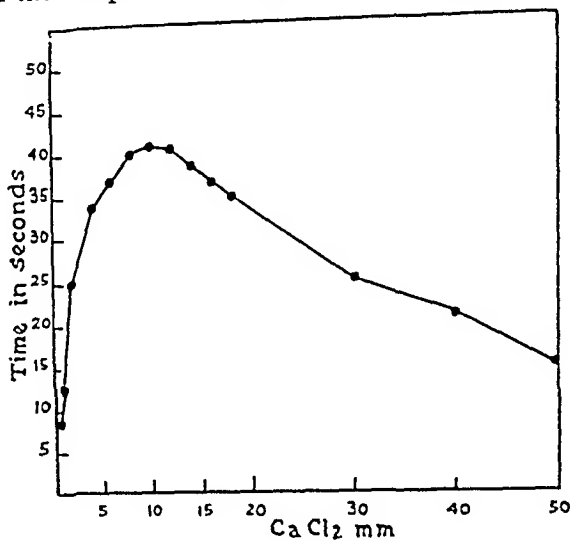


Figure 3. The effect of the concentration of calcium on the consumption of prothrombin. (Plasma was decalcified with Amberlite and mixed with  $\frac{1}{4}$  volume of solution of  $\text{CaCl}_2$  of varying concentrations. The prothrombin time of the serum was determined one hour after the completion of clotting.)

Figure 3 shows an optimal consumption of prothrombin during clotting in a range of concentrations of calcium chloride between 8 and 12 mM. It is then progressively reduced with higher or lower levels. Almost no prothrombin is consumed with a calcium chloride concentration lower than 1 mM. A remarkably high consumption is observed in the samples recalcified with high concentrations of calcium chloride. It must be pointed out, however, that sera from these samples contain a high calcium concentration having a definite inhibitory effect on the prothrombin time. The delay in clotting suggests therefore that a greater percentage of prothrombin has been than actually was used.

An optimal concentration of calcium then appears necessary for the maximum activation of thromboplastinogen. Milstone (16), who likewise believes in the existence of a preliminary phase of the clotting process in which a plasmatic precursor (thrombinokinase) is converted to active thromboplastin, also finds that calcium is necessary for this reaction.

If this is admitted, the mechanism of the action of calcium in the activation of thromboplastinogen is still, however, a matter of speculation. Calcium may act directly as its presence is apparently necessary for the lysis of the agglutination of

platelets (4), which liberates the activator. More probably, however, the meta acts indirectly. Evidence is being accumulated that the so-called »chain reaction« in the coagulation of blood might be due to a labilizing effect of thrombin on the platelets. When the process of coagulation starts, enough thromboplastin would be activated to determine the formation of a little amount of thrombin; this, in turn, would labilize more platelets with consequent activation of more thromboplastin. The chain reaction determines, therefore, an increasingly faster formation of thrombin until clotting is completed (28). Evidence of the labilizing effect of thrombin on the platelets is still mostly indirect. It is known that when the formation of thrombin is deficient no lysis or agglutination of platelets will take place. Agents inhibiting coagulation also retard or prevent platelet disintegration (citratcs, heparin, hirudin, and, to a minor extent, oxalates,<sup>1</sup> and increased platelet stability is noticed in all conditions in which formation of thrombin is either retarded or limited (hemophilia, hypoprothrombinemias, etc.). In these cases little or no activation of thromboplastinogen is observed. Some direct evidence is also being collected. Thus, studies of preparations of slowly centrifuged hemophilic plasma in Silicone-coated chambers under direct microscopical observation show that the introduction of thrombin in the chamber will cause prompt agglutination and clumping of the platelets. If thrombin, therefore, accelerates the disintegration of platelets (and the consequent liberation of thromboplastinogenase), calcium, necessary for the formation of thrombin, becomes an influencing factor of great importance in the activation of thromboplastin.

(2) *The influence of the concentration of calcium on the thrombin-fibrinogen reaction.*

Previous work on the subject has been thoroughly reviewed by Owren (18). The problem is restudied here mostly for uniformity of approach. The thrombin used in our experiments was prepared as directed by Quick. The »full-strength« thrombin, capable of clotting a double volume of oxalated plasma in three seconds, was diluted with an equal volume of distilled water immediately before use to obtain clotting times sufficiently long to permit reliable comparison. Two sources of fibrinogen were used: oxalated plasma, deprothrombinized with tricalcium phosphate as previously described, or a solution of fibrinogen. The latter was prepared according to the following method:

Human oxalated plasma was first deprothrombinized with tricalcium phosphate and then passed through a Seitz filter. Fibrinogen was precipitated with ammonium sulfate at 25 % saturation, the precipitate dissolved in a volume of saline solution equal to that of plasma originally employed and the solution dialyzed in a cellophane bag for twenty-four hours at 40° C. against distilled water, changed repeatedly. Two volumes of this preparation were clotted by one volume of half-diluted thrombin solution in six seconds. The protein content of this solution averaged mg 204 % in several preparations.

To study the influence of calcium on the thrombin-fibrinogen reaction, a series of Pyrex tubes of the internal diameter of 11 mm each containing 0.1 ml of  $\text{CaCl}_2$

<sup>1</sup> The reason why oxalates only partially prevent platelet disintegration can be tentatively explained. Their anticoagulant action, as will be shown later, is slow. A certain amount of thrombin will therefore be formed (with consequent lysis of a number of platelets) before the anticoagulant exercises its full effect.

solution of different molarity were arranged in a water bath at 37° C. To each tube, 0.2 ml of fibrinogen solution or deprothrombinized plasma and 0.1 ml of half-diluted thrombin were added in rapid succession and the clotting time recorded. Each series included a control tube containing 0.1 ml of saline solution.

Figure 4 shows that concentrations of  $\text{CaCl}_2$  higher than 5 mM cause increasing inhibition of the thrombin-fibrinogen reaction. Comparable concentrations of  $\text{SrCl}_2$  determine a similar effect. This suggests that the inhibitory action of cal-

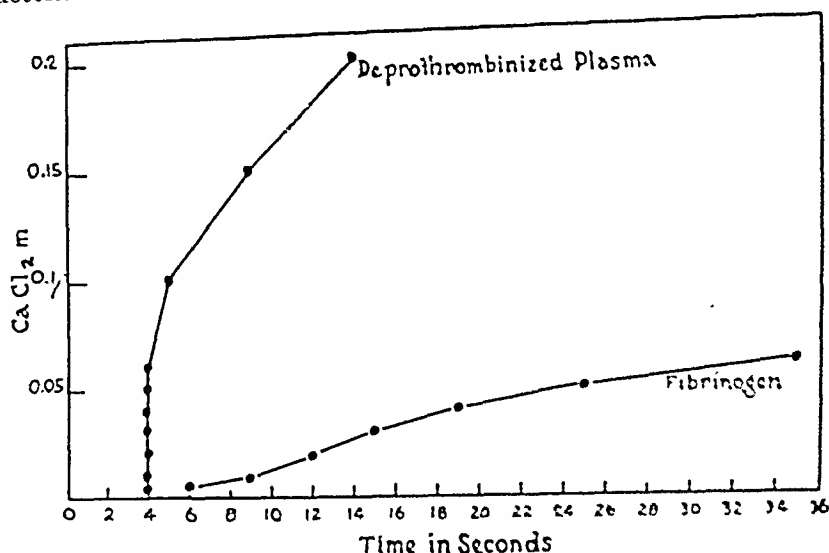


Figure 4. The effect of the concentration of calcium on the thrombin-fibrinogen reaction. (Explanation in the text.)

cium is aspecific. It is probably due to the stabilizing effect on fibrinogen, typical of many salts.

It will be noted that the inhibitory effect of  $\text{CaCl}_2$  is about 20 times weaker when deprothrombinized plasma is used as a source of fibrinogen instead of a directly prepared solution. Deprothrombinized plasma contains, besides fibrinogen, labile factor and probably some other component of the globulin fraction which might influence the speed of the thrombin-fibrinogen reaction. Moreover, its concentration in fibrinogen is higher than that of the solution prepared with the method outlined before.

### The Influence of Calcium on the Stability of Some Factors of Clotting During Storage.

When oxalated human plasma is stored in refrigerator at 4° C. the level and the reactivity of some of the factors active in the process of the coagulation of blood are variably modified. Prothrombin and antithrombin activity appear to be particularly influenced. The former decreases rapidly because of the progressive depletion of the «labile factor» through oxidation (27); the latter markedly increases especially after the fifth day of storage. Some authors (11, 13) also claim that

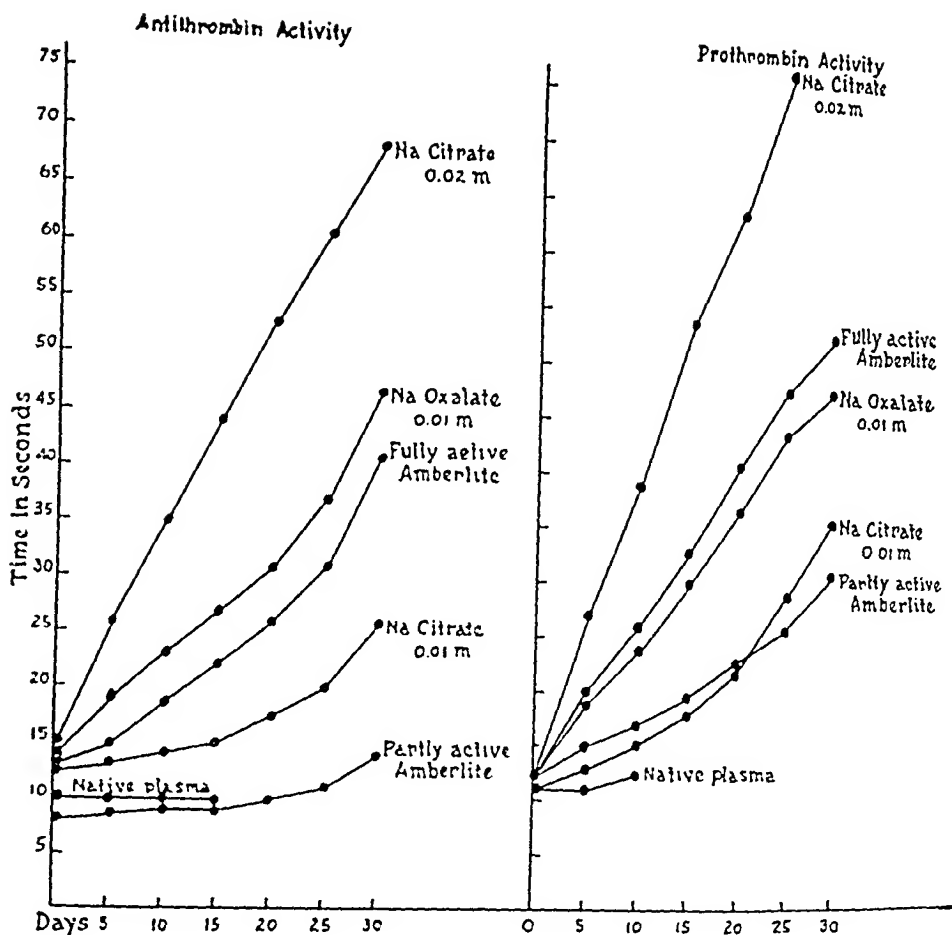


Figure 5. The rise of antithrombin activity and the decrease in prothrombin activity in human stored plasma decalcified with different techniques (average result of several experiments). Oxalated and citrated plasmas were obtained by adding 1 volume of solution of sodium oxalate 0.1 M or of sodium citrate 0.1 or 0.2 M to 9 volumes of blood obtained by venipuncture. The blood was centrifuged at 1,500 r.p.m. for 10 minutes and the plasma collected. «Amberlite plasma» was obtained by centrifugation at 1,500 r.p.m. for 10 minutes from blood decalcified with Amberlite according to the technique previously described; «Native plasma» from blood obtained with Silicone technique. Blood was collected by clean venipuncture through a Silicone-coated needle No. 20. The first ml, collected in an ordinary syringe, was discarded, a syringe coated with Silicone substituted and the necessary quantity of blood collected avoiding foaming. All plasmas were stored at 4° C. in Silicone-coated tubes.)

The data relative to the antithrombin activity of stored plasmas were obtained with the method previously described by the author (37) after an incubation of one minute. The prothrombin activity was measured with the one-stage technique of Quick.

fibrinogen decreases in level and reactivity; but these changes, if they ever occur, appear only after very prolonged storage. Grade and time of appearance of these modifications of coagulability of stored plasma are considerably influenced by the technique of decalcification employed (Figure 5).

As shown in detail in a previous paper (37), the decrease in prothrombin and the rise in antithrombin activities are very pronounced in plasmas decalcified with sodium oxalate 0.01 M or sodium citrate 0.02 M. They are, on the contrary, very limited and of late occurrence in plasma decalcified with sodium citrate 0.01 M

which, furthermore, shows a temporary increase in prothrombin activity in the first 1 or 2 days of storage. Native blood, collected with Silicone technique and centrifuged for 15 minutes at 4,000 r.p.m. yields a plasma which, kept at 4° C. in Silicone-coated tubes, shows a minimal decrease of prothrombin and increase of antithrombin activity until it spontaneously clots. When the blood is decalcified by means of passage through Amberlite, the stability of the «labile factor» and the increase in antithrombin activity are directly related to the amount of calcium left. With a purified resin capable of absorbing all calcium, the plasma will behave during storage as oxalated plasma; when less active Amberlite is employed and part of the calcium is left in the plasma, the «labile factor» is correspondingly more stable and the rise in antithrombin activity limited.

These findings show a clear-cut relationship between coagulability and concentration of calcium in stored plasma. The influence of calcium concentration on the stability of the «labile factor» is evident. Sodium citrate, at a concentration of 0.01 M, apparently leaves enough calcium to assure the stability of the «labile factor». At higher concentrations it not only depresses completely the ionization of calcium but probably also removes calcium combined with some agent active in coagulation, thereby determining marked instability of the «labile factor». Oxalated plasma, in which all the calcium present has been precipitated, presents a great decrease of prothrombin activity during storage. Native plasma, with a normal calcium level, is the most stable during storage. Amberlite plasma, as said before, behaves differently according to the extent of its decalcification.

Equally interesting is the observation that also the rise in antithrombin activity<sup>1</sup> of stored plasma is directly related to the decalcifying agent employed. The increase is maximal in oxalated, highly citrated plasma and plasma treated with a fully active Amberlite and much less pronounced in moderately citrated and native plasma and plasma treated with only partly active Amberlite. The antithrombin activity of these plasmas is considerably reduced by passage of CO<sub>2</sub> for 30'' and likewise its rise is limited and slow when plasmas are stored in atmosphere of CO<sub>2</sub>. No convincing explanation of these findings can be given at present.

The relationship between decalcification of blood and stability of the «labile factor» is important for a full understanding of the rôle of calcium in coagulation. It is possible that the presence of calcium prevents the loss of prothrombin activity because the metal is combined with one or more factors active in the process of coagulation. It is known that, of the non diffusible or combined calcium of plasma, between 30 and 45 % is bound to cephalin (3), a small percentage is probably present as phosphate-protein complex (15) and the rest is combined with proteins.

<sup>1</sup> We found in preliminary work that it is possible to obtain from human plasma stored for thirty days fibrinogen which is still acted upon normally by thrombin at different dilutions. However, in view of the conflicting reports on the subject, a special technique was developed for the determination of antithrombin activity of plasma with which to eliminate errors due to possible changes in the reactivity of fibrinogen during storage. The following method was found to be convenient and reliable: Equal volumes of thrombin and plasma to be studied were incubated in a water bath at 37° C. for variable periods of time (from 1 to 5 minutes). The clot formed was removed by wrapping it about a glass rod coated with Collodion. After the required period of incubation, 0.1 ml of the mixture were added to 0.2 ml of normal oxalated plasma, homologous in species to the plasma tested and freshly drawn, and the clotting time recorded. Full strength thrombin was prepared according to Quick (21) from oxalated human plasma and diluted with distilled water to the concentration required.



As the disappearance of the labile factor from plasma during storage is clearly related to the extent of decalcification, it is logical to conclude that the fraction of calcium active in coagulation of blood is possibly combined with the «labile factor». Evidence that combined and not ionized calcium is the fraction active in the process of coagulation has been accumulating recently and will be presented and discussed in the following chapter.

### Which Fraction of Calcium Is Active in the Process of Coagulation?

Ever since Sabbatani (31) postulated that sodium citrate prevents coagulation of blood by depressing ionization of calcium it has been commonly accepted view that ionized calcium represents the active fraction in the process of clotting. Little further experimental support has been given to this theory. On the contrary observations against it have been repeatedly presented. Vines (44) and Scott and Chamberlain (32) have given particularly strong evidence that calcium is active in coagulation only if combined.

Quick has most brilliantly and consistently challenged the rôle of ionized calcium in coagulation. His previous work on the subject will not be discussed here for consideration of space. Jointly with the author of the present paper, he has recently presented new findings to show the real nature of the fraction of calcium active in the coagulation of blood (26), which will be discussed briefly in this chapter. The conclusion of Quick and Stefanini is again that calcium, irrespective of its state in the circulating blood, is active in the process of clotting only when combined.

This theory is based on several observations. The first is connected with the interpretation of the mechanism of the anticoagulant action of sodium oxalate and sodium citrate. The speed of action of the two anticoagulant agents is completely different. On addition of sodium oxalate, even in quantities greatly in excess of those required to precipitate all calcium, the prothrombin activity of plasma decreases slowly over a long period of time (Figure No. 6). To explain this finding it must be admitted that sodium oxalate not only precipitates ionized calcium from the plasma but also removes calcium from a complex, which is essential for the process of coagulation. This conclusion is also suggested by the well-known observation that, to prevent clotting of blood, an amount of sodium oxalate three times larger than that necessary to precipitate all calcium of blood on a stoichiometric basis is required. On the other side, the anticoagulant action of sodium citrate, which is (as it would be expected) of different grade in relation to the molarity of the salt employed, reaches its maximum effect immediately. It is then obvious that sodium oxalate and sodium citrate prevent coagulation with a completely different mechanism, but a theory to explain the anticoagulant action of sodium citrate is not so easy to formulate as in the case of sodium oxalate. On the basis of some experimental results concerning the absorption of prothrombin components by different gels, Quick and Stefanini have advanced a completely new theory of the mechanism of the anticoagulant action of sodium citrate.

When fresh human plasma made incoagulable by the addition of sodium oxalate

or passage through Amberlite is treated with  $\text{Ca}_3(\text{PO}_4)_2$  gel at optimal concentration according to the technique outlined before, its prothrombin activity is abolished. As previously stated, this effect is due to the complete absorption of prothrombin (27) by the gel (from which it can be quantitatively recovered by elution with sodium citrate). When, however, the plasma has been made incoagulable with sodium citrate or this salt is added to previously oxalated plasma in a con-

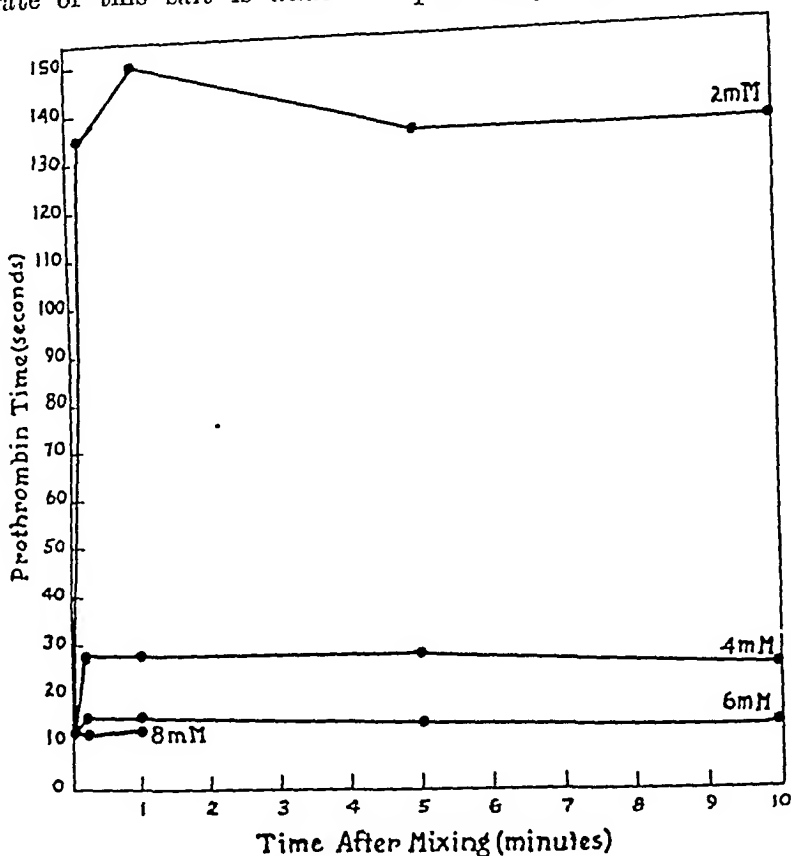


Figure 6. The speed of inhibition of the prothrombin activity by different concentrations of sodium oxalate. (Different volumes of sodium oxalate 0.1 M were added to 1 ml of «native» human plasma in order to obtain the required concentration of the anticoagulant. The prothrombin time was then determined 1, 5 and 10 minutes after mixing.

centration of 12 mM or higher, the absorption of prothrombin by  $\text{Ca}_3(\text{PO}_4)_2$  gel is completely prevented. On recalcification, therefore, a full prothrombin activity can be demonstrated in the treated plasma. Surprisingly,  $\text{SrCl}_2$  and  $\text{MgCl}_2$ , very weak clotting agents when used as «recalcifying» agents for oxalated or Amberlite plasma (41), are only slightly less active than  $\text{CaCl}_2$  for citrated plasma. These results seem to warrant the conclusion that sodium citrate exercises its anticoagulant action not only by depressing the ionization of calcium but also by combining with some factor which is active in coagulation. As prothrombin is usually absorbed by the  $\text{Ca}_3(\text{PO}_4)_2$  gel, while the «labile factor» is not, the evidence points to a combination between citrate and prothrombin. Apparently citrate can be removed from this combination with the addition of  $\text{CaCl}_2$  or any other bivalent ion, with corresponding prompt restitution of prothrombin activity.

The findings: (1) that sodium oxalate acts as an anticoagulant not only by precipitating ionized calcium but also by removing the metal from a complex necessary for the coagulation of blood; (2) that sodium citrate acts as an anticoagulant by combining with components of the prothrombin complex, from which combination it can be removed by the addition of any bivalent ion; (3) that calcium is closely connected with the «labile factor» of prothrombin, as this factor disappears during storage only from plasma from which calcium has been completely removed; all these facts point to the conclusion that calcium is active in coagulation only when combined.

It must be said, however, that some of these conclusions are mostly based on evidence of the indirect type, which leaves space for a different interpretation. As an example, the findings presented do not rule out the possibility that sodium citrate may act as an anticoagulant only by forming a salt with calcium and thereby depressing its ionization. This possibility can be, however, discarded on purely theoretical grounds, as the low concentration of calcium required to determine coagulation and the high dissociation constant of calcium citrate ( $pK$  3.22) (8) make it rather unlikely that the concentration of citrate necessary to inhibit clotting could be sufficient to depress ionic calcium below the level effective for coagulation of blood.

The results based on absorption experiments are also disputable in their significance. As is well known, prothrombin can be absorbed from oxalated plasma by means of several gels:  $Ca_3(PO_4)_2$ ,  $BaSO_4$ ,  $Al(OH)_3$ ,  $Mg(OH)_2$ , each at its own optimal concentration. It is surprising to find that sodium citrate will prevent the absorption of prothrombin by the first two gels only. This finding suggests that the protective action of sodium citrate might be due to its ability to modify some physico-chemical properties of the gels necessary for them to exercise their absorbing activity, and not to the formation of a prothrombin-citrate complex. It is easy to demonstrate that sodium citrate greatly increases the solubility of  $Ca_3(PO_4)_2$  gel while it does not influence, to any appreciable extent, that of the other three gels. This, however, cannot explain the differences in the anti-absorptive properties of sodium citrate, as the influence of the salt on the solubility of  $BaSO_4$  and  $Al(OH)_3$  gels is similar, and yet sodium citrate will prevent the absorption of prothrombin only by the first gel. Differences in specificity of absorption are probably a better explanation for the described finding, as will be discussed in another paper, now being prepared.

Another observation has been made, which might not be explainable with the postulated theory of the mechanism of the anticoagulant action of sodium citrate. It is not usually possible to absorb prothrombin from «native»<sup>1</sup> plasma, as prompt clotting will take place, even when hemophilic plasma is used. We think, however, that the result does not necessarily indicate that the presence of calcium interferes with the absorption of prothrombin by the gels, but only that the contact of the plasma with the foreign surfaces represented by the glass and the gel causes some formation of thrombin and therefore clotting of the plasma, before all prothrombin can be absorbed by the gel.

In conclusion, all the findings presented on the problem of the nature of calcium

<sup>1</sup> Collected with Silicone technique, without addition of anticoagulants.

which is active in coagulation of blood seem to indicate clearly that calcium is active only when combined. Findings presented in detail in this paper indicate the possibility of the existence of a «calcium-labile factor» complex. The exact rôle of this complex in the process of coagulation of blood and even the clear demonstration of its existence obviously require further work based on a more direct experimental approach and probably on entirely new techniques.

### Summary.

The introduction of new techniques in the study of blood coagulation has offered new possibilities for the study of the rôle of calcium in the clotting of blood. These new methods consist in the use of «Silicone», a film with which blood can be kept incoagulable for a long time without any alteration of its properties or lysis of platelets, and of Amberlite IR-100, a resin which quantitatively removes calcium from the blood. The combination of the two methods permits one to obtain *in vitro* blood not different from that circulating *in vivo* with the exception of the complete removal of calcium. The further addition of measured amounts of calcium under different experimental conditions permits one to study with unprecedented accuracy the influence of calcium on the different phases of coagulation and on the process *in toto*.

The most important results obtained with the use of these techniques can be summarized as follows:

1. The calcium level optimal for coagulation of whole blood or plasma is of 1.5 mM, practically identical to that of circulating blood; that for optimal conversion of prothrombin to thrombin of 2.5 to 10 mM. Calcium is the most effective clotting agent but its action is aspecific as also possessed by strontium and, to a much lesser extent, by magnesium. All these cations exercise an inhibitory effect at concentrations higher than the optimal one.

2. All three phases of the coagulation process appear to be influenced by calcium, in artificial experimental conditions. Optimal activation of thromboplastin, *in vitro*, as expressed by the results of the prothrombin consumption test, requires a  $\text{CaCl}_2$  concentration of 8—12 mM; optimal action of thrombin on fibrinogen takes place at  $\text{CaCl}_2$  level lower than 5 mM. Calcium is most active in the phase of clotting leading to the formation of thrombin from prothrombin.

3. Decrease of prothrombin activity, due to the progressive disappearance of the «labile factor», and rise of the antithrombin activity during storage are closely related to the presence or absence of calcium, as they are maximum in plasmas made incoagulable with addition of sodium oxalate, sodium citrate 0.02 M or passage through highly active Amberlite and much less pronounced in plasmas made incoagulable with sodium citrate 0.01 M or passage through only partially active Amberlite. The influence of calcium on the stability of the «labile factor» seems to indicate the existence of a «calcium-labile factor complex».

4. Evidence is presented that: a) sodium oxalate acts as anticoagulant not only by precipitating calcium, but also by removing the metal from a combination with a factor indispensable for the normality of the clotting process; b) sodium citrate

inhibits coagulation by combining with one or more factors of the prothrombin complex in which it can be substituted by any bivalent cation (Ca, Sr, Mg). From this evidence and the one presented in the previous paragraph it is concluded that combined and not ionized calcium is the fraction active in coagulation of blood.

### Acknowledgments.

The author is greatly indebted to Dr. Arman J. Quick, under whose supervision and with whose cooperation great part of this work has been carried out. The author also wishes to express his thanks to Mr. Leo C. Massopust, Department of Art and Photography, Marquette University School of Medicine, who kindly prepared the figures accompanying the article.

### References.

1. Bendien, V. M., Snapper, I.: *Bioch. Z.* **260**, 639, 1933. — 2. Clark, E. P., Collip, I. B.: *J. Biol. Chem.* **63**, 461, 1925. — 3. Drinker, N., Zinsser, H. H., *J. Biol. Chem.* **143**, 764, 1942. — 4. Ferguson, J. H.: *Am. J. Physiol.* **108**, 670, 1934. — 5. Ferguson, J. H.: *Physiol. Rev.* **16**, 640, 1936. — 6. Ferguson, J. H.: *Am. J. Physiol.*, **119**, 755, 1937. — 7. Greville, G. D., Lehmann, H., *J. Physiol.* **103**, 175, 1944. — 8. Hastings, A. B., Mac Lean, F. C., Eichelberg, J. L., Hall, J. L., Da Costa, E.: *J. Biol. Chem.* **107**, 351, 1934. — 9. Horne, R. M.: *J. Physiol.* **19**, 356, 1896. — 10. Jaques, L. B., Fidler, E., Feldstedt, E. T., Mac Donald, A. G.: *Can. Med. Ass. J.* **55**, 26, 1946. — 11. Lavergne, G. H., Lavergne Poindessault, B.: *Compt. r. Soc. Biol.* **135**, 1199, 1941. — 12. Loomis, E. C., Seegers, W. H.: *Arch. Biochem.* **5**, 265, 1944. — 13. Loomis, E. C., Seegers, W. H.: *Am. J. Physiol.* **148**, 563, 1947. — 14. Mac Lean, F. C., Hastings, A. B.: *J. Biol. Chem.* **108**, 285, 1934. — 15. Masket, A. V., Chanutin, A., Ludwig, S.: *J. Biol. Chem.* **143**, 764, 1942. — 16. Milstone, J. H.: *J. Gen. Physiol.* **31**, 301, 1948. — 17. Nordbö, R.: *Skand. Arch. f. Physiol.* **75**, suppl. 11, 1936. — 18. Owren, P. A.: *Acta Med. Scand.* suppl. 194, 1946. — 19. Quick, A. J.: *Proc. Soc. Exp. Biol. & Med.* **40**, 206, 1939. — 20. Quick, A. J.: *ibidem* **42**, 788, 1939. — 21. Quick, A. J.: «The hemorrhagic diseases and the physiology of hemostasis». Charles C. Thomas, Publ., Springfield, Ill. 1942. — 22. Quick, A. J.: *Am. J. Med. Sc.* **214**, 272, 1947. — 23. Quick, A. J.: *Lancet* **2**, 397, 1947. — 24. Quick, A. J.: *Science* **106**, 591, 1947. — 25. Quick, A. J., Stefanini, M.: *Proc. Soc. Exp. Biol. & Med.* **67**, 111, 1948. — 26. Quick, A. J., Stefanini, M.: *J. Gen. Physiol.* **32**, 190, 1948. — 27. Quick, A. J., Stefanini, M.: *J. Lab. & Clin. Med.* **33**, 819, 1948. — 28. Quick, A. J., Shanberge, J. N., Stefanini, M.: *Am. J. Med. Sc.* **217**, 198, 1949. — 29. Ransmeier, J. C., Mac Lean, F. C.: *Am. J. Physiol.* **121**, 488, 1938. — 30. Ravdin, I. S., Riegel, C., Morrison, J. L.: *Arch. Surg.* **91**, 801, 1930. — 31. Sabbatani, M. L.: *Compt. r. et mem. Soc. Biol.*, Paris **54**, 716, 1902. — 32. Scott, F. H., Chamberlain, C.: *Proc. Soc. Exp. Biol. & Med.* **31**, 1054, 1934. — 33. Snyder, M.: *J. Kansas Med. Soc.* **35**, 289, 1934. — 34. Stassano, H., Dumas, A.: *Compt. r. Acad. Sc.* **150**, 937, 1924. — 35. Stefanini, M.: *Policlinico (Sez. med.)* **53**, 82, 1946. — 36. Stefanini, M.: «Master Thesis, Marquette University, Milwaukee, USA», 1947. — 37. Stefanini, M.: *Am. J. Clin. Path.* **18**, 527, 1948. — 38. Stefanini, M.: *Proc. Soc. Exp. Biol. & Med.* **67**, 22, 1948. — 39. Stefanini, M.: *Medicine* **27**, 377, 1948. — 40. Stefanini, M.: *Policlinico (Sez. prat.)* **55**, 1298, 1948. — 41. Stefanini, M., Quick, A. J.: *Am. J. Physiol.* **152**, 389, 1948. — 42. Steinberg, A.: *Proc. Soc. Exp. Biol. & Med.* **56**, 124, 1944. — 43. Stewart, J. K., Pohle, F. J.: *Ibidem* **39**, 532, 1938. — 44. Vines, H. W. C.: *J. Physiol.* **55**, 86, 1921.

From the Departments of Physiology and Medicine, Birmingham University  
(Great Britain).

## **An Investigation of the Hypothesis of Tubular Excretory Mass, $T_m$ .**

By

J. A. BARCLAY, W. T. COOKE<sup>1</sup> and G. de MURALT.<sup>2</sup>

(Submitted for publication June 28, 1949.)

In 1938, Smith, Goldring and Chasis (1) put forward the important hypothesis that there was a limit to the amount of solute that could be excreted or absorbed in unit time by the renal tubules in man and, furthermore, that this limited amount was directly related to the number of actively functioning tubules. They termed this quantitative measurement the tubular mass,  $T_m$ , and, since the capacity of the tubules for reabsorption or secretion was therefore limited, they also pointed out that  $T_m$  must be independent of the glomerular filtration rate and plasma level of the solute, provided all the tubules were fully saturated. Others (2 & 3) have questioned the validity of this hypothesis and in the course of our own investigations, results have been encountered which could not be reconciled with Smith's theory. The amount of diodone or para-amino-hippuric acid, excreted per minute by the tubules (*i. e.* the tubular excretory mass) at varying plasma levels has therefore been reinvestigated.

### **Material and Methods.**

Eight females and two males (aged 20—53 years) formed the subjects for these experiments. Three were healthy medical students, four had hypertension without clinical evidence of kidney damage, two had chronic and one subacute glomerulonephritis. The experiments were carried out with the patients recumbent, after a light lunch. Inulin and diodone or para-amino-hippuric acid were administered in normal saline by intravenous infusion at a rate of 10—14 ml per minute. Urine was collected by an indwelling catheter and the clearance periods terminated by irriga-

<sup>1</sup> Queen Elisabeth Hospital, Birmingham 15 (Great Britain).

<sup>2</sup> British Council Scholar, 1947—1948.

tion with 20 ml distilled water. The experiments lasted from 2½ to 4 hours and the amount of fluid infused varied from 1,500 to 2,000 ml. The plasma level was kept within narrow limits for at least two periods of 15 minutes before being raised or allowed to fall. The general procedure is illustrated by two experiments in the Appendix. Tubular mass was calculated according to the usual formula. At the high plasma levels of diodone and para-amino-hippuric acid that were attained, the extent of »binding» was not checked, but according to Smith and Smith (4), the amount of free diodone increases with increasing plasma values. In calculating  $T_m$ , 0.73 has been used as the factor  $F$ . W. for diodone and 0.83 for para-amino-hippuric acid. Consequently, the values for  $T_m$  at high plasma levels may be even lower than those given. The experimental procedure did not cause any vasomotor collapse, pyrogenic reaction, undue anxiety or discomfort, other than that associated with an indwelling catheter and continuous intravenous drip. Recoveries of inulin were not affected by high concentration of diodone or para-amino-hippuric acid.

## Results.

In all experiments, at or just after the highest plasma level, the values for  $T_m$  diminished in amounts varying from 24 to 124 per cent. of the maximum observed figure. The results are given in detail in Table 1, and illustrated in Figures 1 and 2.

## Discussion.

These results are not in accord with the hypothesis that there is a limited secretory capacity of the tubules. Of the possible explanations, errors inherent in the methods and techniques may be of sufficient magnitude to make the estimation of  $T_m$  difficult or, alternatively, the concept itself may be in error.

In the calculation of tubular mass, accurate estimation of the glomerular filtration rate is essential. At low plasma levels of diodone, errors in  $G$ .  $F$ .  $R$ . will make no significant alteration in calculated figure but at high plasma levels when the amount of diodone filtered may exceed that secreted by the tubules, small errors will cause great variations in the value for  $T_m$ . Errors in the actual estimation of inulin are those of the biochemical method used and should not be playing any part in the production of our results for essentially similar findings result if creatinine clearances are used as a measure of glomerular filtration rate. Errors in urine collection, however, can cause marked variation in a clearance or  $T_m$  calculation. The part played by such errors can be checked to some extent by plotting the diodone/inulin concentration ratios against the plasma level when the ratios will be seen to diminish smoothly as the plasma levels increase. Averaging successive periods will also diminish the effects of errors in urine collection and in Figures 1 and 2 are plotted such averages of three successive periods so that each clearance period represents the average clearance over 40 to 60 minutes. The resultant curves show that the value for  $T_m$  is closely dependent upon the plasma

Table 1.  
*Hypertension.*

	Period	Time	Volume per min.	Inulin Clearance	Creatinine Clearance	Urea Clearance	Plasma Iodine	Urine Con- centration	Tm
Case 1. Male Age 45. S. A. 1.71	1	13	4.4	41.5	57	56	12	440	16
	2	11	4.4	75	75	65	12	660	23
	3	16	6.0	120	126	100	12	1,000	49
	4	37	5.7	114	106	94	24	1,950	91
	5	16	4.9	92	79	69	46	1,900	62
	6	13	10.0	142	100	122	82	1,400	55
	7	12	13.9	124	111	134	89	980	55
Case 2. Female Age 53. S. A. 1.95	1	15	11	106	143	69	48	700	40
	2	15	19	208	209	65	54	900	89
	3	10	18	152	126	56	59	600	42
	4	16	16	134	135	62	140	800	— 9
	5	14	13	128	105	61	131	750	—23
	6	10	8	67	100	90	124	1,120	29
Case 3. Female Age 36. S. A. 1.44	1	11	9.2	77	106	116	6	420	35
	2	10	13.4	84	93	96	6	270	32
	3	10	13.4	84	93	74	6	270	32
	4	9	13.9	83	80	65	10	325	39
	5	10	12.5	85	87	78	15	325	31
	6	10	8.0	77	74	56	18	470	27
	7	8	9.4	91	72	76	21	400	
	8	14	9.6	76	66	70	87	760	25
	9	9	13.1	90	62	76	81	600	25
	10	11	6.9	56	40	49	67	620	15
	11	10	10.0	97	51	73	52	700	33
	12	10	12.3	75	80	81	40	500	39
	13	10	12.5	77	115	79	28	450	40
Case 4. Female Age 24. S. A. 1.76	1	22	5.4	63	147	56	39	1,510	63
	2	14	7.6	88	126	53	52	1,430	75
	3	15	12	119	113	71	79	1,040	56
	4	11	13.7	120	133	76	147	1,050	15
	5	25	13.4	90	52	67	151	850	10
	6	16	5.6	101	99	45	120	1,670	4
	7	20	4.5	104	75	51	94	2,150	25

level of diodone or para-amino-hippuric acid and does not maintain a constant level.

Ekehorn (2) has criticized the original paper put out by Smith, Goldring and Chasis (1) on account of the inadequacy of its data. There is perhaps some justification for this criticism since the only case, presented as a figure, shows that Tm falls as plasma level rises. Further and more extensive data has been provided by Brun and his colleagues (5 and 6). From their results, it is clear that the values for Tm remain relatively constant and reproducible in normal subjects if the plasma diodone levels are kept between 20 and 30 mg per cent. Josephsen (3), on the other hand, when using a single injection technique, encountered so many anomalous results, that he concluded that in damaged kidneys, Tm was not a valid measurement of functioning kidney tissue. Others (7 and 8), too, have en-



Table 1 (continued).

*Normal Subjects.*

	Period	Time	Volume per min.	Inulin Clearance	Creatinine Clearance	Urea Clearance	Plasma Iodine	Urine Con- centration	Tm
<i>Case 6</i> Female Age 20. S. A. 1.77	1	15	6.2	155	150	113	1.7	500	29
	2	15	6.2	185	145	107	1.7	320	17
	3	21	7.5	159	130	102	11.0	960	59
	4	15	9.0	129	120	100	31	1,300	88
	5	15	9.5	150	130	105	37	1,450	97
	6	15	9.7	120	120	97	44	1,350	92
	7	22	12.0	125	126	108	46	1,025	81
	8	19	15.8	148	130	107	40	750	74
	9	16	12.5	109	132	99	37	900	83
	10	16	8.1	90	120	109	32	1,250	80
	11	17	6.8	89	120	64	21	1,370	79
	12	19	5.2	102	110	47	9	1,450	60
<i>Case 7.</i> Female Age 21. S. A. 1.68	1	13	5.2	118	119	75	22	1,500	59
	2	17	3.7	96	75	53	22	1,570	43
	3	15	5.8	128	105	66	21	1,350	59
	4	19	13.6	145	129	102	20	640	66
	5	11	20	140	145	114	36	450	53
	6	14	18.2	125	132	107	55	510	43
	7	13	13.4	134	128	100	70	840	41
	8	15	10.6	130	126	91	81	1,100	41
	9	21	6.4	84	93	51	66	1,370	47
	10	23	4.9	79	94	61	43	1,650	56
<i>Case 8.</i> Female Age 21. S. A. 1.76 P. A. H.	1	20	10		131	96	65	665	
	2	15	9.6	102	105	91	71	1,620	94
	3	34	3.8	72	52	44	82	1,880	22
	4	21	8.8	162	120	75	78	1,700	45
	5	15	9.0	107	98	80	71	2,340	87
	6	25	6.0	100	96	77	49	2,116	57
	7	15	4.8	94	91	56	29	1,770	62
	8	28	3.1	76	90	43	15	1,770	45

countered negative values for Tm in kidneys damaged temporarily either in the experimental animal or in the human kidney. In several patients with pyelonephritis, Raaschou (1948) (10) encountered inconstant values for Tm which tended to increase with the continuation of the experiment (as for example Case 9 of the present series). He was unable to account for his findings on technical grounds and though he had no unequivocal explanation, he considered that diffusion of diodrast from normal to diseased poorly vascularised tissues provided a possible underlying mechanism. Examination of his figures shows similarities to the present experiments, Tm tending to increase as plasma levels decrease.

There is then published evidence that in diseased kidneys Smith's hypothesis does not always hold good. The experiments we are reporting are consistent with such reports but since the plasma levels have been on the average much higher than those hitherto reported, the more evident changes in Tm may well be explained. The possible importance of the height of the plasma level is well illustrated by one of the normal subjects (Case 6). In Fig. 2, the averaged results are given from which it could be stated that Tm is constant between the levels of 25 and 45.

Table 1 (continued).  
*Glomerulo-Nephritis.*

	Period	Time	Volume per min.	Inulin Clearance	Creatinine Clearance	Urea Clearance	Plasma Iodine	Urine Con- centration	Tm
<i>Case 5.</i> Female Age 38. S. A. 1.80	1	16	5.6	81		98	6	1,300	69
	2	11	5.9	121		66	6	900	57
	3	18	5.5	94		55	30	1,400	57
	4	11	4.5	68		49	73	1,600	35
	5	13	5.5	101		54	72	1,500	29
	6	14	4.7	126		57	65	1,600	16
	7	17	3.3	86		43	50	2,100	37
	8	29	2.2	51		36	32	2,700	47
	9	16	4	50			18	2,100	70
<i>Case 9.</i> Female Age 18. S. A. 1.47	1	10	16.3	160			7	200	23
	2	10	17.1	94			17	413	57
	3	10	15.3	140			24	503	49
	4	15	10.0	70			32	508	32
	5	11	8.7	40			60	662	37
	6	12	7.5	50			76	975	41
	7	4	11.0	80			84	1,175	
	8	11	5.5	47			90	1,287	29
	9	10	6.9	69			74	1,362	51
	10	10	9.4	98			56	1,040	62
	11	10	6.9	98			38	1,525	74
	12	10	8.3	149			20	1,562	103
<i>Case 10.</i> Male Age 32. S. A. 1.9	1	11	6.7	200		84	10	1,680	95
	2	9	6.1	160		60	11	1,780	93
	3	12	7.8	195		78	15	1,050	59
	4	11	8.2	160		61	23	975	49
	5	8	8.3	160		62	27	1,050	51
	6	12	5.7	120		49	41	1,425	40
	7	10	7.7	168		57	39	1,300	45
	8	9	6.9	200		51	37	1,425	37
	9	11	6.0	166		59	34	1,575	49
	10	12	5.6	215		48	27	1,550	40
	11	20	4.7	235		47	20	1,740	42
	12	20	4.4	205		44	10	1,560	52

The individual clearance periods, however, show that the maximum clearance is reached at 37 and thereafter falls away, and with the findings in the other nine cases in mind, the plasma level should have been raised to still higher levels to confirm or disprove the constancy of Tm in this case.

Further clues can be found from our experiments by plotting the diodone or para-amino-hippuric acid/inulin concentration ratios against plasma level. In Fig. 3 the values for case 3 have been so plotted. In this experiment, inulin clearance remained relatively constant and averaged 80 ml per minute. Using this inulin clearance and taking arbitrary plasma values and Tm values of 20, 40 and 60 mg per minute, the theoretical curves for diodone/inulin concentration ratios may be plotted against the plasma level. The resultant curves cut all possible theoretical lines. Furthermore, with increasing plasma levels, the curve obtained is a true physiological self depression and is clearly distinguishable from the theoretical curve which is only an arithmetical depression. It is of interest that

this curve is practically identical to that given by Smith and Ratner (11) for the iopax-inulin clearance ratios against the plasma level of iopax. However, the actual curve fails to fit the possible theoretical curves admitted by the hypothesis.

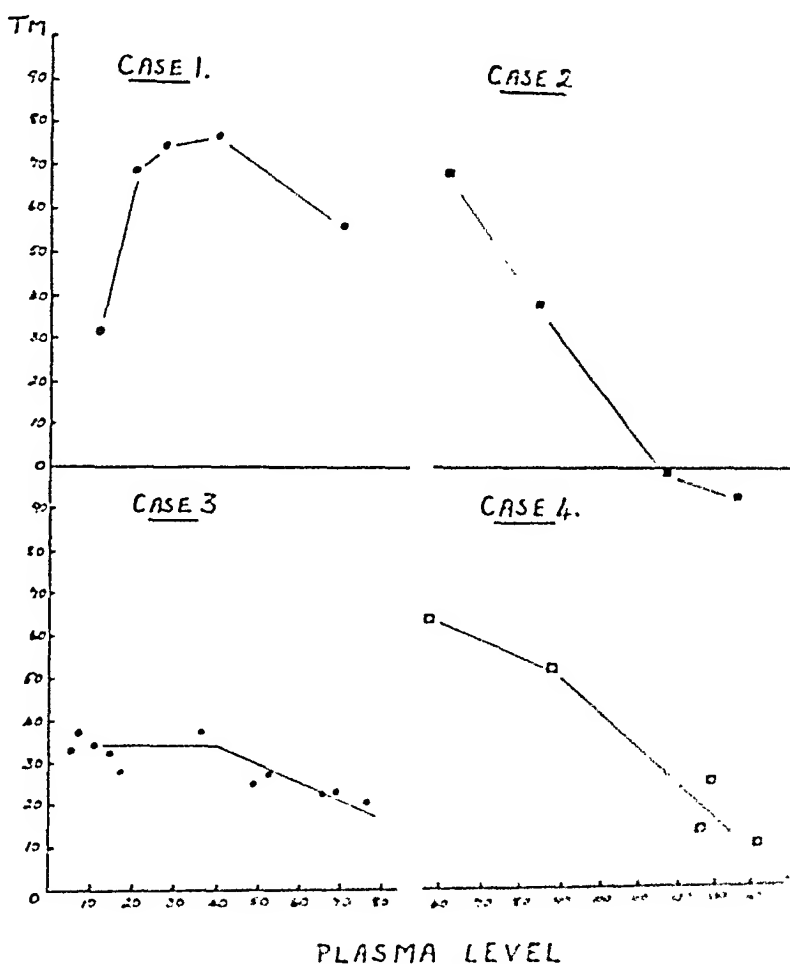


Fig. 1. Cases 1, 2, 3 and 4. Hypertension without clinical evidence of Kidney Disease. Each point represents the average of three successive periods. Depression of the value for  $T_m$  is seen in each case at high plasma levels.

In three cases the ratio fell below 1, a finding also noted by Josephson. We would agree with him that the most likely explanation is that part of the filtered diodone is reabsorbed. Since the phenomenon is reversible, it may be tentatively suggested that this reversal of flow is the result of the high concentration of the solute in the tubular lumen and consequent upset of the normal concentration gradients. It is doubtful, however, whether this can be the whole explanation. Newman (12) and his colleagues have demonstrated numerous other inconsistencies in the behaviour of diodone at plasma levels at which its clearance should increase with plasma flow.

In conclusion, our own experience allied with other reports in the literature

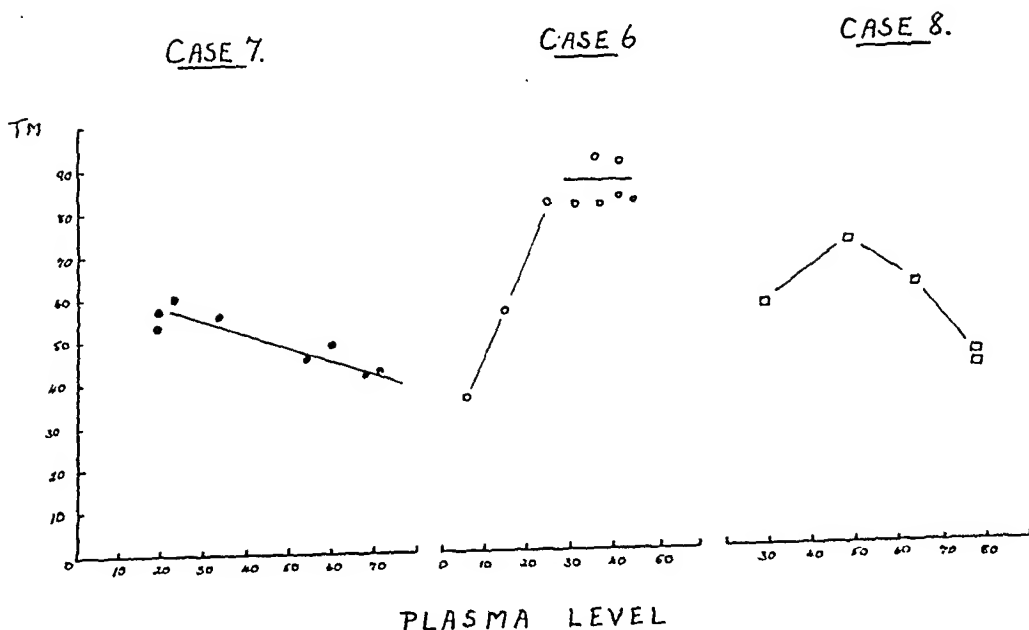


Fig. 2. Normal Controls. Case 6 and 7 Diodone. Case 8 Para-amino-hippuric acid. Each point represents the average of three successive periods.

lead us to suppose that at present there is no easy way of determining Tm. Furthermore, the question as to whether any constant measure of kidney mass can ever be determined still remains to be answered.

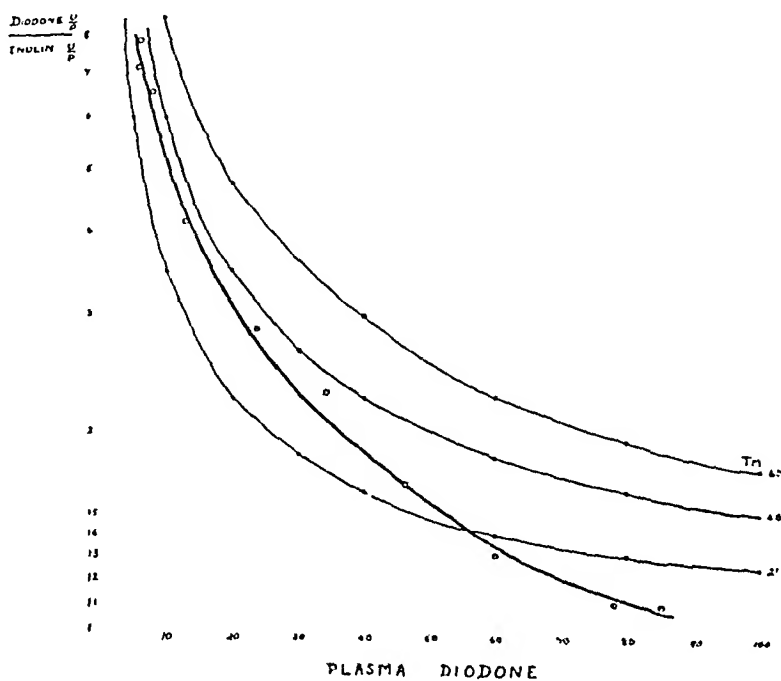


Fig. 3. Curves showing the determination diodone/inulin concentration ratios plotted against the plasma level in Case 3 (open o). With inulin clearance concentration at 80 ml per minute, three graphs theoretically true if the Tm hypothesis be correct, are shown with Tm, levels of 20, 40 and 60 mg per min. and arbitrary plasma levels at the corresponding diodone/inulin concentration ratios (closed ●). It will be seen that the actual curve cannot be fitted to the theoretical curves.

## Appendix I.

*Case 3.* Zero time. Blank blood and commencement i. v. drip 500 ml saline + 6 ml 50 p. c. diodone + 25 ml 10 p. c. inulin. 40 min. Discard urine. 42 min. Blood I. 51 min. Urine I. 61 min. Urine II. 70 min. Blood II. 71 min. Urine III. Second bottle 500 ml saline + 6 ml 50 p. c. diodone and 25 ml 10 p. c. inulin. 72 min. 2 ml 50 p. c. diodone i. v. 78 min. Blood III. 80 min. Urine IV. 90 min. Urine V. 100 min. Urine VI. 108 min. Urine VII. 111 min. Blood IV. 112—114 min. 20 ml 50 p. c. diodone i. v. 117 min. 3rd bottle 500 ml saline + 25 ml inulin + 20 ml 50 p. c. diodone. 120 min. Blood V. 122 min. Urine VIII. 131 min. Urine IX. 142 min. Urine X. 152 min. Urine XI. 162 min. Urine XII. 170 min. Urine XIII. 173 min. Blood VI. Completion of intravenous drip.

*Case 6.* Zero time. Blank blood, i. v. drip 500 ml saline + 5 ml 50 p. c. diodone + 25 ml diodone. 31 min. Urine discard. 35 min. Blood I. 46 min. Urine I. 61 min. Urine II. 65 min. Blood II. 70 min. Second 500 ml saline + 25 ml inulin + 32 ml 50 p. c. diodone + i. v. dose 5 ml 50 p. c. diodone. 82 min. Urine III. 86 min. Blood III. 97 min. Urine IV. 112 min. Urine V. 127 min. Urine VI. 131 min. Blood IV. 135 min. Third 500 ml saline + 25 ml inulin + 16 ml 50 p. c. diodone. 149 min. Urine VII. 160 min. Blood V. 168 min. Urine VIII. 184 min. Urine IX. 185 min. End of Drip. 186 min. Blood VI. 200 min. Urine X. 217 min. Urine XI. 225 min. Blood VII. 236 min. Urine XII.

## Appendix II.

Inulin was measured by the method of Findlay and White (5), Para-amino-hippuric acid by the method given by Barclay, Cooke and Kenney (13), Diodone and Creatinine by the methods of Barclay and Kenney (14, 15) and Urea by the micro method of Conway and O'Malley (16). The formula used for calculating Tm was that given by Smith, Chasis and Goldring (1).

$T_m = \text{Amount in Urine} - \text{Amount filtered per unit time} = UV - FW C_{in} P$  where U and P are the concentrations in mg per cent. of the secreted substance in urine and blood,  $C_{in}$  the clearance of inulin, F the fraction of the substance free and available for filtration and W the fraction of water in the plasma.

## References.

1. Smith, H. W., Goldring, W., Chasis, H.: *J. Clin. Invest.*, 1938, 17, 263. — 2. Ekehorn G.: *Acta Med. Scand.*, 1946, 124, 282. — 3. Josephson, J.: *Acta Med. Scand.*, 1947, 128, 515. — 4. Smith, H. W., and Smith, W.: *J. Biol. Chem.*, 1938, 124, 107. — 5. Brun, C., Hilden, T., Raaschou, F.: *Acta Med. Scand.*, 1947, 127, 464. — 6. Brun, C., Hilden, T., Raaschou, F.: *Acta Pharmacol.*, 1947, 3, 1. — 7. Bobey, M., Longley, L. P., Dickes, R., Price, W., and Hayman, J.: *Amer. J. Physiol.* 139, 155, 1943. — 8. Redish, J., West, J. R., Whitehead, B. W., Chasis, H.: *J. Clin. Invest.* 1947, 26, 1043. — 9. Raaschou, F.: *Studies on Chronic Pyelo-nephritis*; Copenhagen, 1948. — 10. Smith, W. W., Ranges, H.: *Am. J. Physiol.*, 1938, 123, 720. — 11. Newman, E., Kattey, A., Genecin, A., Gerast, J., Calkins, E., Murphy, S.: *Bull. J. Hopkins*, 1949, 84, 135. — 12. Findlay, T., and White, H. L.: *Proc. Exp. Med. and Biol.*, 1940, 45, 623. — 13. Barclay, J. A., Cooke, W. T., Kenney, R. A.: *J. Physiol.*, 1946, 106 P. — 14. Barclay, J. A., and Kenney, R. A.: *Biochem. J.*, 1945, 39, 375. — 15. Barclay, J. A., Kenney, R. A.: *Biochem. J.*, 1947, 41, 586. — 16. Conway, E. J., O'Malley, E. O.: *Biochem. J.* 1942, 36, 655.

From the Pathology Department, Ancoats Hospital, Manchester 4, Great Britain.

## The Secretion of Reticulocytes by the Normoblast.

By

FREDERIC DURAN-JORDA.

(Submitted for publication June 28, 1949.)

---

### Normoblast Secretion of Reticulocytes.

To observe how hemopoiesis takes place in the human embryo, a set of embryos about 1 mm in size were studied in serial sections, so that the appearance and relationship of the normoblasts and red blood corpuscles present therein would be little affected by mechanical processes.

The red blood corpuscles contained in the sections contrasted in size with the normoblasts, which varied from a very small cell ( $4.5 \mu$ ) consisting almost entirely of a nucleus surrounded by a small halo of cytoplasm, to a cell ( $16.6 \mu$ ), almost four times as large. The fully developed normoblasts were not homogeneous cells, but appeared to have a compound structure (figs. 1—3). Some normoblasts were breaking off parts of their cytoplasm, and in some cases the size of these broken portions corresponded to the size of a red blood corpuscle (figs. 4—7). These observations were accepted as genuine facts because of the numerous times the phenomenon was observed. It could not have been produced by the mechanics of smearing because the observations were made in sections. In a few cases, remnants of normoblast cytoplasm of a considerable size could be found ( $15.4 \mu$  average diameter), one in particular having a volume corresponding to 4.4 red blood corpuscles (fig. 8).

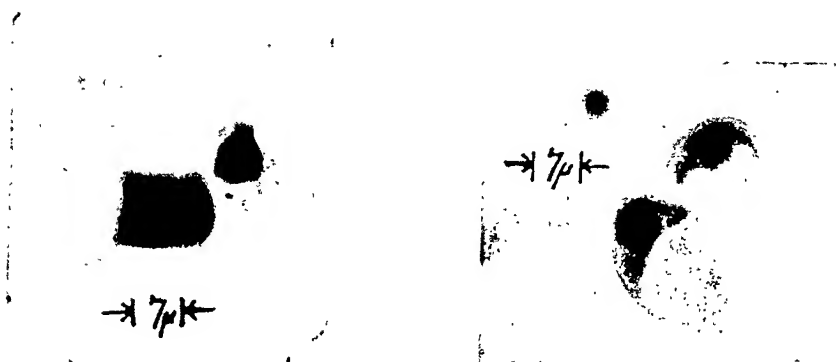
In order to study the comparative volumes between the red blood corpuscles and different nucleated red blood corpuscles, the following method was used. The cells were measured with a micrometer ocular, and the red blood corpuscle was taken to have an average volume of 88.8 cu.  $\mu$ . Any nucleated red cell to be compared with this was measured in several diameters to calculate the approximate area of the cell, but to obtain the volume the average thickness of the cell was accepted as only  $2.1 \mu$ . This measurement corresponds to the thickness of an anu-

cleated red blood corpuscle, therefore any cell which includes a nucleus will always be thicker, so that the volume of any nucleated cell estimated in this way always gives a smaller volume than it has in reality.

*Sections stained with haematoxylin and eosin. (Figs. 1—8).*



Fig. 1. Human embryo. Arrow points to a red blood corpuscle.



Figs. 2 and 3. Sequence of normoblasts from a human embryo in the process of growing. In fig. 3 the large normoblast has a volume 10 times bigger than a red blood corpuscle.

### *Example:*

Taking a nucleated red cell with minimum diameter of  $14\mu$  and maximum diameter of  $16.8\mu$ , the average diameter will be  $15.4\mu$  which gives an average radius of  $7.7\mu$

The volume  $= \pi \times (7.7)^2 \times 2.1 = 391.1$  cu.  $\mu$ .

$$\frac{\text{vol. of cell}}{\text{vol of r. b. c.}} = \frac{391.1}{88.8} = 4.4 \text{ red blood corpuscles.}$$

The accompanying pictures suggested that the red blood corpuscles in the human embryo were produced by a cytoplasmic extrusion from the normoblast, which afterwards became a very small cell composed practically of only a nucleus with a tiny halo of eosinophil cytoplasm.

In previous studies (Duran-Jorda 1943, 1947), hemopoiesis was divided into two

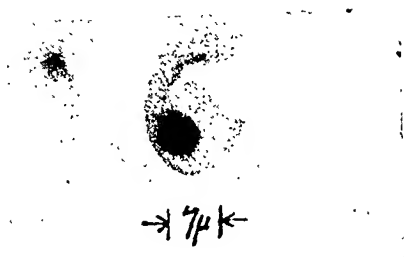


Fig. 4.



Fig. 5.

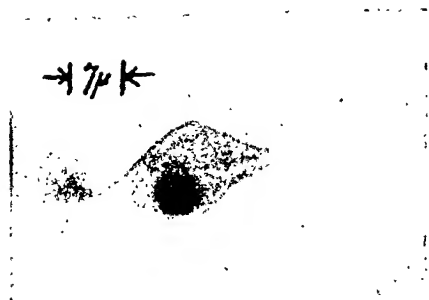


Fig. 6.



Fig. 7.

Figs. 4—7. Human embryo. Normoblasts breaking out parts of their cytoplasm.

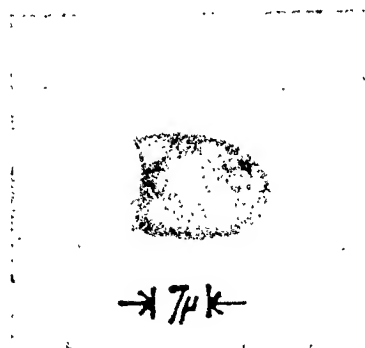


Fig. 8. Human embryo. Cytoplasmatic portion of a normoblast with a volume equivalent to 4.1 red blood corpuscles.

processes, one the extra-uterine, which was a secretion by the eosinophil polymorph and is responsible for 99 % of red blood corpuscles; the other, described as the intra-uterine process, accounts for blood formation in the embryo, but in the adult, this process secretes only 1 % of red blood corpuscles, represented by the reticulocytes.

In order to study the origin of the reticulocytes from an objective point of view,



*Smears from human adult bone marrows, stained with cresyl blue and May Grunwald-Giemsa. Figs. 9-22.*



Fig. 9.

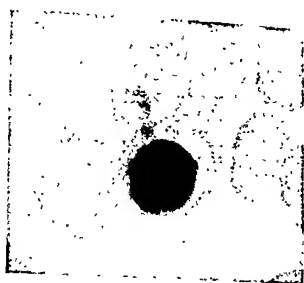


Fig. 10.



Fig. 11.



Fig. 12.

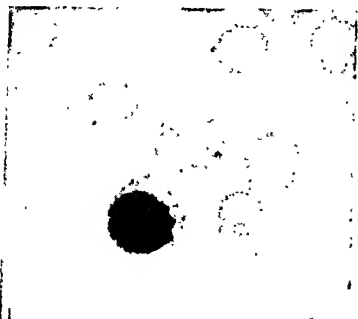


Fig. 13.



Fig. 14.

a systematic study of 150 sternal bone marrows was carried out, and the blood smears were stained with a differentiating triple stain to show the nature of the red blood corpuscles.

### Technique.

Some very clean slides were smeared with cresyl-blue in a 0.5 % alcohol solution, and the stain was allowed to dry on the slide. A drop of bone marrow blood was smeared on top of the stain and then covered quickly by a Petri dish to prevent quick drying, so that the reticulocytes would have time to pick up the cresyl blue. After 3 min. the lid of the Petri dish was removed, the slide dried quickly in the air

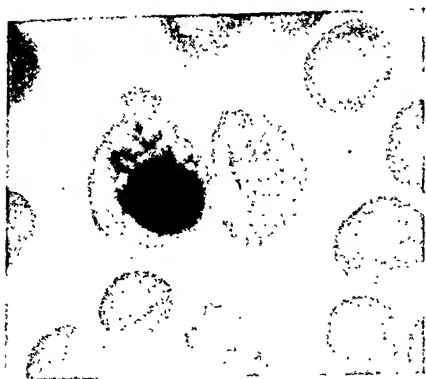


Fig. 15.

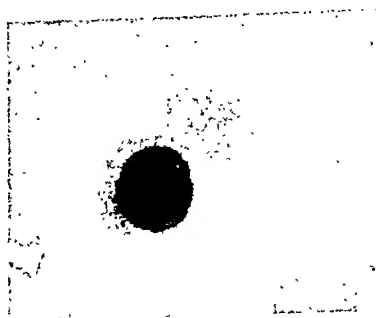


Fig. 16.

Figs. 9—16. Reticulocytes alongside normoblasts. Some are still attached together by a cytoplasmic bridge.



Fig. 17. One normoblast attached with a long string of cytoplasm to two reticulocytes.

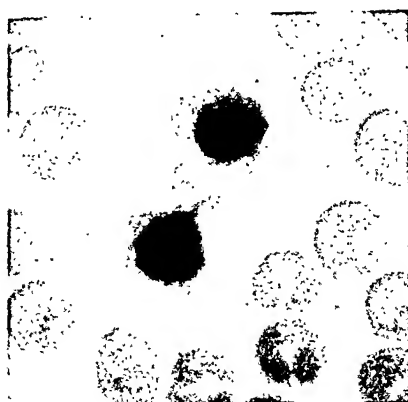


Fig. 18. Two normoblasts showing a very ragged cytoplasm.

and then stained with May Grunwald-Giemsa. If the drop of blood was too thick, the cresyl-blue produced a form of agglutination of the red blood corpuscles and made the slide very difficult to study. It was necessary, therefore, that the drop should be more on the small side than on the large.

On these adult bone marrows, similar observations were made to those made in the embryo, the only difference being that many bone marrows were required to arrive at the same conclusions. It could be seen that the very tiny normoblasts, which have been described as expelled nuclei, were really in a number of cases, only nuclei surrounded by a very small halo of eosinophil cytoplasm.

The normoblasts presented a wide range of sizes, but in megaloblastic bone marrows the hemopoietic cells were large enough ( $20\ \mu$  diameter) to contain about 9.4 red blood corpuscles. In this case, the comparative volumes were worked out by the method described previously.

The use of the triple stain was very effective for studying the relation between the normoblast and the reticulocytes, and after a large number of bone marrow investigations, it became apparent that many normoblasts appeared in the neighbourhood of reticulocytes, or vice-versa.



Fig. 19. Nucleus of an undefined cell surrounded by about 7 reticulocytes. Some of the reticulocytes are still enveloped in the mitochondria of the cytoplasm of the cell.

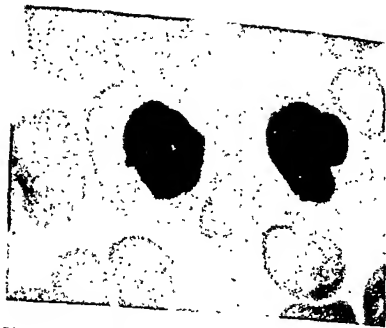


Fig. 20. Two megaloblasts with a volume equivalent to 6 and 4 red blood corpuscles, respectively.



Fig. 21. Polymorph megaloblast with a volume equivalent to 12 red blood corpuscles.



Fig. 22. Karyokinesis of the normoblast producing two fully developed normoblast daughters.

In some microscopical fields, the normoblast appeared in the region of from one to three reticulocytes, and in other fields, the normoblast formed the centre of attraction of an agglutinated body of two or three reticulocytes. Some fields showed a normoblast immediately alongside a reticulocyte. Where the normoblast and the reticulocyte were side-by-side, they were sometimes attached together, forming one cellular body. This union was regarded sceptically at first in case it turned out to be two cells superimposed, but the following facts supported the interpretation that the phenomenon was really a mechanism of normoblast secretion.

A free reticulocyte had a circular shape similar to a non-reticulated red blood corpuscle, but the shape of the reticulocyte attached to a normoblast had an ab-

normal raggedness. This was not considered to be the result of any process of agglutination as only normoblasts and reticulocytes which had a margin of separation from the other cells were studied, in order to avoid any possibility of exterior pressure, and the surrounding red blood corpuscles had retained their proper shape, which contrasted with the unevenness of the reticulocyte attached to the normoblast.

After staining with the triple stain it was taken as a sign of a genuine secretion that the normoblast and reticulocyte should show the same shade of orange, which contrasted not only with the red blood corpuscles around them but also with any neighbouring normoblasts and reticulocytes.

In every case the appearance of the reticulation present in a particular normoblast and reticulocyte pair was the same, and in some instances, it could be seen that the reticular material was still linking the two bodies. As far as could be observed under different microscopical foci, the bridge which joined the two bodies appeared to be a genuine one.

A fact also in favour of secretion was that mathematically, a normoblast attached to a reticulocyte should not be found as frequently as it is in a normal bone marrow (figs. 9, 17).

*Example:*

In a normal bone marrow, there can be calculated in every cmm of blood:

4,950,000 red blood corpuscles

45,000 white blood corpuscles

5,000 nucleated red cells (which have been taken to be all normoblasts)

50,000 reticulocytes

Having picked out a normoblast, the mathematical chances governing the nature of the adjacent cells are as follows, in every 1,010 cells:

Normoblast	1.
white blood corpuscles	9.
reticulocytes	10.
red blood corpuscles	990.

These being the simple proportions in which the cells occur in the bone marrow. It will be seen, therefore, that the chances in favour of a normoblast being together with a red blood corpuscle as against a reticulocyte are as 990 : 10.

Some normoblasts had a very ragged cytoplasm with ragged portions broken off, but it was very difficult to conclude that this was a mechanical defect as normoblasts found in neighbouring fields and red blood corpuscles had a normal aspect (fig. 18).

In pathological bone marrows of patients with very grave anemia of different types (normoblastic and megaloblastic) and who had less than 1 million red blood corpuscles, the secretion of the reticulocytes appeared to be carried out in bulk by some cells which were always destroyed by the mechanism of smearing, leaving behind a nucleus difficult to classify as belonging to any particular type, and surrounded by a group of reticulocytes which all had the same characteristics and were

still wrapped in remnants of mitochondria from the destroyed cell (fig. 19). If the bone marrow contained large numbers of megaloblasts, two facts were found to be worth reporting. One was the huge size of some of the megaloblasts, which had a volume large enough to contain 9.4 red blood corpuscles, and the other was that some of them were not mononuclear but appeared more like polymorphonuclear cells (figs. 20—21).

The previous observations described in the adult bone marrow of the secretion of the reticulocyte by the normoblast, are in every way similar to the observations previously seen in the embryo, and support the interpretation of the fact that in the embryo, the normoblast secretes the red blood corpuscles.

The phenomenon of cytoplasmatic extrusion appears to be not only exclusive to the normoblast but can also be seen occasionally in different bone marrow cells, myeloblast and lymphocyte, which extrude parts of their cytoplasm.

Another fact worth mentioning which can be easily appreciated in bone marrow investigations, is that the normoblast with an eosinophilic cytoplasm divides into two normoblast daughter cells which have the same characteristics as the parent cell. This demonstrates that some normoblasts are produced as such, and do not require any previous step of maturation from hematocytoblast and pro-normoblast to become a normoblast.

### Summary.

1. In the human embryo the normoblast nucleus always appears to be surrounded by a halo of cytoplasm.
2. The normoblast attains a volume equivalent to 10 red blood corpuscles.
3. The red blood corpuscles of the embryo are a product of normoblast extrusion.
4. In different human bone marrows, a sequence of normoblasts of various sizes can be followed, similar to that seen in the embryo.
5. By the use of a triple stain, it can be seen how the normoblast secretes the reticulocyte in the human bone marrow.
6. In bone marrows with a megaloblastic reaction, it is possible to demonstrate the existence of megaloblasts, some with a polymorph nucleus, and with a cytoplasm able to contain 10 red blood corpuscles.
7. The author also stresses the fact that the hemoglobinized normoblast divides and produces two fully developed normoblast daughters.

I am very grateful to Professor Wood Jones for his constructive discussions on this work, and also to the Physicians of Ancoats Hospital for their kind co-operation with patients; not forgetting Mr. Jeffrey B. Dean, B. Sc., to whom I owe very many thanks for the photomicrographs.

### Bibliography.

1. Duran-Jorda, F. (1943) *Lancet* ii, 186. — 2. Duran-Jorda, F. (1947) *Nature*, London, 159, 293.

From the Physical Laboratory and the Department of Medicine, University of Utrecht, Holland.

## The Influence of Distance on the Pitch of the Percussion Note.

By

H. C. BURGER, D. Sc. and F. L. J. JORDAN, M. D.

(Submitted for publication July 16, 1949.)

For an appreciation of the percussion sounds of the thorax, the distance of the examiner's ear from the wall of the thorax is important. Selling (1907) pointed out that in the lecture room the difference in percussion notes was more easily observed by those students who sat further away than by those sitting nearer. He concluded that the resonant note over the lungs which is heard over a greater distance than the dull percussion note, has a greater amplitude and this was confirmed by Fahr and Brandi (1929). The practice of »threshold percussion» is also based on this conclusion and in this method which aims to outline the more or less dull zones on the thorax (relative and absolute cardiac dullness), the ear is placed at such a distance that the duller note is no longer observed.

Selling believed that the differences in frequency were responsible for this phenomenon. Stumpf (1883) and Lucae (1904) had already found that low notes are more easily observed at a greater distance than high notes. In the lung sounds which can be heard more easily at a greater distance, the lower frequencies are better represented than in the duller percussion notes where the higher frequencies originating from the pleximeter predominate. At a distance, however, the higher frequencies are not weakened as much as the lower ones, so that the phenomena discussed by Selling are based exclusively on a difference in amplitude. Landes (1940) proved that high notes supersede the lower ones. He compared the percussion note with a microphone at a distance of 15 cm from the chest wall with the one at 50 cm. In the graphs made with the microphone at a distance of 15 cm from the chest wall, vibrations of 70—80 Hertz (Hz) occurred (»cavitary vibrations») as well as those of about 170—230 Hz. At a distance of 50 cm these higher frequencies which arise in the lungs appear to their full advantage. The fact

that the examiner's ear should not be too close to the thorax for the observation of a beautiful lung note, was therefore supported by Landes' experiments.

Landes (1940) tried to explain this by interference-phenomena which are said to occur in the thorax due to the connection between the space in the thorax and the outside. These interference phenomena would have their influence chiefly on the lower frequencies.

It is, however, not necessary to assume such a complicated mechanism. A simple model of the vibrating thorax enables us to explain the phenomena observed.

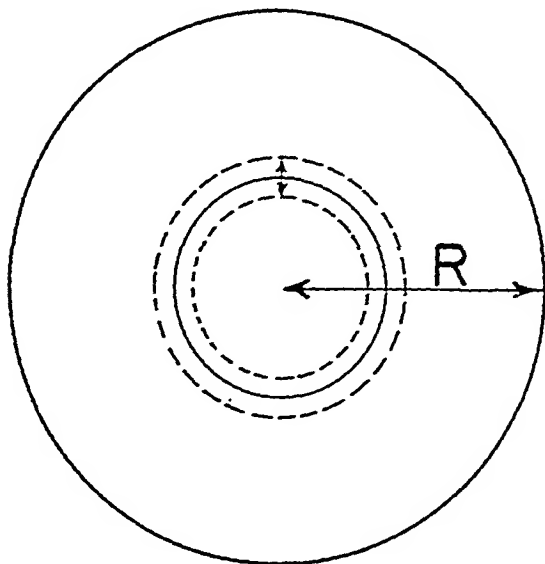


Fig. 1. A sphere growing alternately bigger and smaller, pulsating between the dotted positions. The sound-intensity on a sphere with a radius of  $R$  is asked.

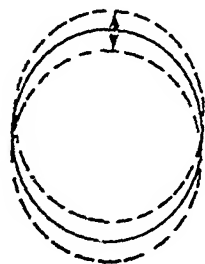


Fig. 2. A sphere moves backwards and forwards between the dotted positions, while the radius remains constant.

A computation of sound radiation is only possible for a mathematically simple form of the radiating body. Therefore the thorax is approximated by a sphere with a diameter of 20 cm. There are two simple ways in which a sphere may vibrate, viz. one in which the centre remains stationary while the radius increases and decreases periodically (Fig. 1), and another in which the radius remains constant while the centre moves periodically (Fig. 2). Neither of these vibrations gives a good idea of what happens during percussion.

In this case the chest wall would vibrate but the back would not move at all. This is shown by obtaining mean values of the movements represented in Figs. 1 and 2. As the sound radiation may be computed in both cases (Rayleigh, 1896), the average can also be treated theoretically.

The result of it is reported here though we shall omit the computation. The intensity of sound decreases with increasing distance from the chest wall. This has been shown by plotting the decrease of intensity in decibels on the ordinate, when we go with ear or microphone from the immediate vicinity of the chest wall (distance = 0) to points further away from it. (Fig. 3.)

This figure shows that the decrease in intensity amounts to much more in the low notes (50 Hz) than in the high ones (400 Hz). An increase of the distance from 10 to 60 cm decreases the intensity of the low note 9 db more than that of higher ones. This theoretical result may explain the fact that with greater distance the note grows appreciably higher on account of the relative weakening of the lower components.

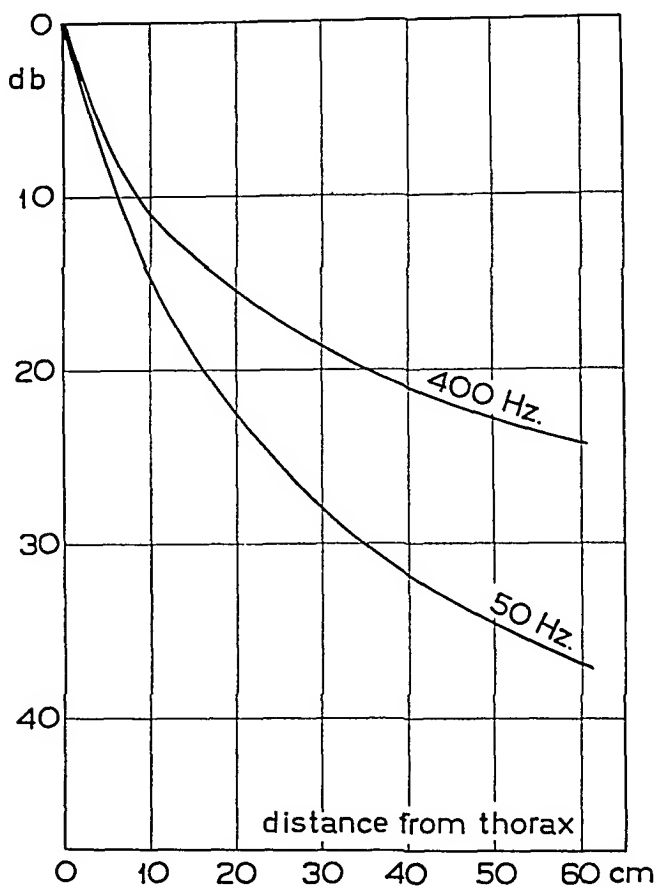


Fig. 3. Decrease of intensity in decibels of the percussion sound at various distances from the ear to the thorax.

This may also be described in a less exact way. If we suppose that the source of the sound under discussion is a vibrating sphere (Fig. 1), pulsating periodically between the two dotted positions, the problem becomes simplified. In the case of great frequencies the disturbance of the equilibrium (= sound) spreading in all directions, will decrease in intensity according to the law that intensity is inversely proportional to the square of the distance  $R$  from the centre of the sphere. This is obvious from the consideration that the energy of sound which is being transmitted, is distributed over spheres of increasing size, and consequently the energy passing per  $\text{cm}^2$  per second becomes smaller, inversely proportional to the surface  $4\pi R^2$  of these spheres.

If the frequency, however, is small, the inertia of the air will hardly be noticeable near the pulsating sphere. The air spreads radially and back again to the



sphere while this becomes bigger and smaller in turn. A quantity of air, independent of the radius  $R$  of the spherical surface, passes through a large spherical surface which surrounds everything. Consequently the velocity of the air is inversely proportional to  $R^2$ . As the intensity of sound is proportional to the square of the amplitude (= velocity), this intensity will be inversely proportional to  $(R^2)^2 = R^4$ .

When the frequency is smaller and the distance is increased the intensity of sound decreases far more rapidly (proportional to  $1/R^4$ ) than it does in great frequencies (proportional to  $1/R^2$ ). Consequently the low tones are relatively weak further away and the resulting sound is higher.

Apart from this purely physical phenomenon we must not forget that the two terms pitch and frequency are not identical. The difference between these terms is so slight when a sound like the one we hear during percussion is concerned that we must assume that the fact that a percussion note sounds higher further away from the thorax, must be explained physically in the way described above. The observations of Landes (1940) confirm this theory.

### Summary.

The percussion note is higher further away from the thorax than nearer. This is explained by purely physical considerations.

### References.

1. Fahr and Brandi, *Dtsch. Arch. klin. Med.* 164, 1, 1929. — 2. Landes, *Dtsch. Arch. klin. Med.* 185, 116, 1940. — 3. Lucae, *Arch. Physiol.* 1904, Suppl., p. 400. — 4. Rayleigh, «The theory of Sound», II, 1896, p. 247. — 5. Selling, *Dtsch. Arch. klin. Med.* 90, 163, 1907. — 6. Stumpf, «Tonphysiologie», I, p. 208, Leipzig, 1883.
-

From the Medical Department III, Kommunehospitalet, Copenhagen (Director: Poul Iversen, M. D.), the State Serum Institute, Copenhagen (Director: Jeppe Ørskov, M. D.), and the Medical Department B Bispebjerg Hospital, Copenhagen (Director: Professor E. Meulengracht, M. D.).

## Steroid Hormones in Hepatitis.

By

M. BJØRNEBOE, CHR. HAMBURGER and M. JERSILD.

(Submitted for publication July 23, 1949.)

A very marked increase in the incidence of chronic hepatitis occurred in Denmark during the years 1944—1946 (1—5), but it was remarkable that the disease was found almost exclusively among women past the menopause.

Because it was thought that investigations into the metabolism of oestrogenic hormones in these patients might help to explain this peculiar phenomenon, experiments were designed in collaboration between Dept. III of Kommunehospitalet (M. B.), Dept. B. of Bispebjerg Hospital (M. J.) and the Hormone Dept. of the State Serum Institute (C. H.).

Several animal experiments and clinical observations suggested that the liver plays an important part in the metabolism of oestrogenic hormones. Zondek (1934) (6, 7) found that oestrogens are rapidly destroyed in the body and that in vitro they are inactivated by minced liver tissue, whereas tissue from other organs was ineffective.

Further evidence was produced by Israel et al. (1937) (8), who by heart-lung-liver perfusion experiments showed that oestrogenic substances are inactivated only when the liver is included in the system. Several experiments have shown that oestrogens have little or no effect when they have to pass through the portal system, before reaching their destination, *i. e.* uterus, vagina etc. When ovaries are implanted subcutaneously in castrated female rats, the typical oestrous reaction is seen in the vagina, but not when they are implanted in the mesentery (Golden and Severinghaus, 1938) (9). On the other hand, pellets of oestrogenic substances implanted in the spleens of adult castrated female rats produce oestrus only for a brief period and then become ineffective, but when the blood is diverted from the spleen directly into the systemic circulation, the specific action of the hormones reappears (Biskind, 1941) (10). Pedersen-Bjergaard (1939) (11) found

that in castrated rats 10 times the amount of oestrone is required to produce oestrus when it is injected into a mesenteric vein than when injected into the femoral vein. Most of the hormone disappeared when passing through the liver. The comparatively slight effect of the genuine oestrogens when taken by mouth is also due to hepatic inactivation. When severe damage of the liver is produced experimentally such as by poisoning with carbon tetrachloride, the amount of endogenous oestrogens in the blood is increased more than in the control animals, apparently because the poisoned liver is no longer capable of inactivating the hormone. An enhanced effect of exogenous oestrogens was demonstrated in adult rats poisoned with carbon tetrachloride by Pincus and Martin (1940) (12).

The inactivation of oestrogenic hormones by the liver explains several observations in human pathology. As early as 1932, Silvestrini (13) described gynaecomastia in patients who had cirrhosis of the liver. The same phenomenon has been observed by Edmondson et al. (1939) (15), Morrione (1944) (16), Rather (1947) (17) and Lloyd and Williams (1948) (18). Several cases of gynaecomastia were noticed amongst concentration camp prisoners from World War II, presumably because malnutrition had caused insufficiency of the liver (Jacobs, 1948) (14). The failure of the damaged liver to inactivate the endogenous oestrogens causes a rise in these substances resulting in mammary and testicular abnormalities (15–18). Bean (1943, 1945) (19–20) drew attention to the spider naevi which are found in insufficiency of the liver often together with erythema palmaris, telangiectases in the mucosa of the nasopharynx and the rectum, etc. It is reasonable to assume that these symptoms are due to an increase in the circulating oestrogenic hormones, the more so because the symptoms are aggravated by the administration of oestrogens. Furthermore, the urinary excretion of oestrogenic substances has been claimed to be increased in young men suffering from acute hepatic disease (Gilder and Hoagland, 1946) (21), and in men suffering from chronic hepatic disease (Glass et al. 1940) (22), but it must be admitted that the assay of these small amounts of oestrogens is inaccurate.

In women suffering from hepatic insufficiency the following symptoms occur apart from the already mentioned skin and mucosal vascular disturbances: post-menopausal uterine bleeding, hyperplasia of the endometrium and an abnormally high excretion of oestrogenic substances. The normal variations in the oestrogen excretion during the menopause were thought to obscure the interpretation of the urinary analyses, and in post-menopausal women the exact quantitative determination of the urinary oestrogens is of necessity unreliable. We therefore investigated the metabolism of oestrogenic hormones by giving large quantities of oestrone by mouth and afterwards determining the oestrogen excretion. Such experiments had been performed in male patients with hepatic cirrhosis by Glass et al. (1940) (22); the recovery was very high, the total values ranging from 83 to 86 per cent of the injected dose in 3 of 4 patients. In July 1947, when our own investigations were almost completed Zondek and Black (1947) (23) published the results of their oestrone clearance tests in women suffering from hepatitis. Stealy and Stimmel (1948) (24) made similar investigations.

### Original Investigations.

The investigations include the determination of urinary oestrogens in a group of 11 women suffering from chronic hepatitis and a control group of 12 women past the menopause with various diseases not likely to influence the liver function. Both groups received large quantities of oestrone by mouth. The 17-ketosteroids were estimated in 11 men and one woman suffering from acute hepatitis.

#### (1) Oestrogenic substances

All the patients were given a single dose of 100,000 I. U. of oestrone (10 tablets of a commercial preparation, Ovex Leo). The urine was collected for exactly 24 hours following the administration of oestrone and the oestrogenic substances were estimated, the total amount was measured after acid hydrolysis and benzene extraction, and the content of »free» oestrogens was determined in the untreated or diluted urine.

The biological method of assay was used, the cornification of the vaginal epithelium of adult spayed mice being the criterion of response. Most of the oestrogenic substances in the urine are normally linked to glycuronic acid or sulphuric acid, and only a small amount is found as »free» oestrogen. The conjugation takes place presumably in the liver.

Oily solutions of the benzene extracts were used for the determination of the total amount of oestrone and the mice were given 3 subcutaneous injections in 48 hours. In the assay of the non-conjugated oestrogens the mice were given 5 subcutaneous injections of the original urine for a period of 48 hours. The mouse units were converted into international units of oestrone on the basis of the dose-response curves for oestrone in oily and watery solutions.

The results (Table 1) show clearly that the patients with cirrhosis have, on the

Table 1.

*Oestrogenic substances excreted during the first 24 hours in urine collected after the oral administration of 100,000 I. U. of oestrone to patients with chronic hepatitis and to controls.*

I. U. of oestrogens per 24 hours.

Patients with hepatitis		Controls	
total	free	total	free
96,000	3,600	96,000	2,000
90,000	2,300	75,000	10,800
75,000	13,500	48,000	2,000
60,000	9,000	24,000	3,600
42,000	6,500	24,000	1,800
36,000	2,000	24,000	1,600
30,000	18,000	24,000	1,600
30,000	2,500	21,000	3,200
21,000	13,000	12,000	3,600
21,000	4,500	12,000	3,600
12,000	5,800	6,000	900
		600	250
Averages: 47,000	7,300	30,600	2,900

average, excreted more of the oestrogen administered than the control patients; this applies especially to the »free» oestrogens. Considering the variability of the values obtained, the difference between the two groups is not marked. The number of assays is not large enough to allow of a satisfactory statistical analysis of the figures and the technique used does not indicate the type of oestrogen found. Several investigations into the metabolism of the oestrogens have proved that the organism is capable of converting oestrone into oestradiol and oestriol (Pincus and Pearlman 1942 (25); Schiller 1945 (26)), but it is not known whether the metabolism follows the same lines in patients with hepatic insufficiency as in individuals with normal liver function. As the biological activity of the various oestrogens differs considerably, a fair evaluation of the results is difficult, but the higher oestrogen excretion in the cirrhotic patients suggests an impaired inactivation of oestrogens. Our results agree with those of Zondek and Black (1947) (23), who found an increased amount of oestrogen in the blood from patients with hepatic disease 4 hours after the injection of 250,000 I. U. of oestrone and also an increased urinary oestrogen excretion. The impaired oestrone clearance was only observed in patients with advanced cirrhosis; of the other liver function tests the production of urea was closely related to the oestrone clearance.

## (2) 17-Ketosteroids

The most important 17-ketosteroids in the urine are androsterone, etiocholanolone and dehydroandrosterone. In women they are produced exclusively by the adrenal cortex, but in men also by the testicles. The excretion is therefore higher in males than in females. The amount excreted daily increases during puberty and reaches its maximum in the middle of the twenties; during the next decades the excretion diminishes gradually. Very high values are found in tumours or in hyperplasia of the adrenal cortex and lowest values in patients with Addison's disease and panhypopituitarism (Simmonds' disease). Values just below normal are frequent in patients with chronic debility.

The 17-ketosteroids produce a red-violet colour with meta-dinitrobenzene (Zimmermann's reaction) and the assay in the urine is easy to perform and reliable. Gilder and Hoagland (1946) (21) found decreased 17-ketosteroid excretion in early acute hepatitis; the values gradually rose during convalescence and reached the normal level 20 to 50 days after the onset of the disease. We have performed a similar investigation in 11 men and one woman suffering from hepatitis (Fig. 1). About the normal values and the technique employed the reader is referred to Hamburger's papers (1948 a, b) (27). On the average the 17-ketosteroid excretion was found to be considerably lower during the first 2—3 weeks of the disease much below the lowest normal values, but during the next few weeks the excretion rose to values within the normal range; one of the patients had, however, very low values as late as 10 weeks after the beginning of the illness. This patient had severe hepatitis with jaundice lasting 4 months. We thus confirmed the findings of Gilder and Hoagland (21) that the 17-ketosteroid curve follows the course of the disease.

The low 17-ketosteroid level at the beginning of infectious hepatitis might be

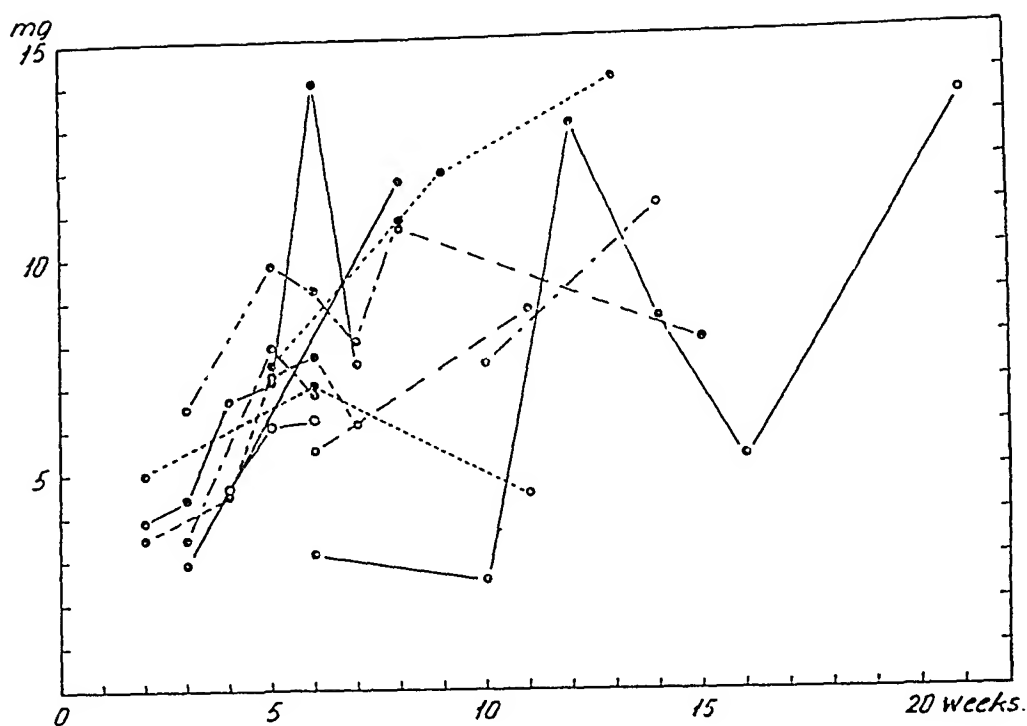


Fig. 1. Excretion of 17-ketosteroids during the course of acute hepatitis in 11 male (●) and 1 female patients (○), (ordinate: mg 17-ketosteroids excreted in 24 hours; abscissa: weeks from the beginning of symptoms).

interpreted as secondary to the increased amount of oestrogen in the organism. Such an antagonism between the male and female sex hormones is generally accepted and is thought to be due to the reciprocal gonad-pituitary relationship. The antagonism would explain the clinical finding of testicular atrophy in cases of hepatitis. Gilder and Hoagland (21), however, did not accept this hypothesis since the restoration of the 17-ketosteroid values preceded the fall of the abnormally high oestrogen output. The cause of the low 17-ketosteroid excretion might also be in the liver disease itself, but it would then be difficult to explain why the damaged liver function results in high oestrogen and low 17-ketosteroid excretion. The most reasonable interpretation of the findings is, that the low 17-ketosteroid values are due not so much to the impairment of the liver function as to the reaction of the organism to damaging stimuli. Forbes et al. (1947) (28) and others have shown conclusively that the 17-ketosteroid level normally responds to all kinds of bodily injury (trauma or acute disease) by a transient increase of one or a few days' duration followed by a marked depression and a gradual return to the normal values during convalescence.

Although our investigations have provided no answer to the question why the cases of chronic hepatitis in Denmark a few years ago almost exclusively occurred in women past the menopause, our findings support the view that the liver plays a part in the normal metabolism of the steroid hormones. For the present the biological assay of the urinary excretion of the oestrogenic substances and the

chemical test for 17-ketosteroids are of little value as a means of evaluating the liver function.

### Summary.

The urinary excretion of oestrogenic substances was determined biologically in 11 female patients suffering from cirrhosis of the liver and in controls after the oral administration of 100,000 I. U. of oestrone.

The patients with hepatic disease excreted on the average a higher proportion of the hormone given than the controls particularly in the form of non-conjugated (free) oestrogens.

The 17-ketosteroid excretion in the urine was followed in 11 male and one female patient with acute hepatitis. The values were low in the early stages of the disease and rose to normal values during convalescence.

Our findings did not provide an explanation of the peculiar phenomenon that the cases of chronic hepatitis during the epidemic in Denmark in 1944-46 almost exclusively were found among women past the menopause.

### References.

- 1) Bjørneboe, M. and Brøchner-Mortensen, K.: *Ugeskrift Laeger*, 107, 715 (1945). —
- 2) Jersild, M.: *Ibid.*, p. 819 (1945). — 3) Jersild, M.: *New Engl. J. Med.*, 237, 8 (1947). —
- 4) Alsted, G.: *Amer. J. med. Sc.*, 213, 257 (1947). — 5) Bjørneboe, M., Jersild, M., Lundbæk, K., Hess Thaysen, E. and Ryssing, E.: *Lancet*, I, 867 (1948). — 6) Zondek, B.: *Scand. Arch. Physiol.*, 70, 133 (1934). — 7) Zondek, B.: *Lancet*, II, 356 (1934). — 8) Israel, S. L., Meranze, D. R. and Johnston, C. G.: *Amer. J. med. Sc.* 194, 385 (1937). — 9) Golden, J. B. and Sevringhaus, E. L.: *Proc. Soc. Exp. Biol. Med.*, N. Y., 39, 361 (1938). — 10) Biskind, G. F.: *Endocrinology*, 28, 894 (1941). — 11) Pedersen-Bjergaard, K.: »Comparative studies concerning the strengths of oestrogenic substances». Oxford University Press, London 1939. — 12) Pincus, G. and Martin, D. W.: *Endocrinology*, 27, 838 (1940). — 13) Silvestrini, R.: *Diagnosi*, Fasc. 13-14 (1923). — 14) Jacobs, E. C.: *Ann. int. Med.* 28, 792 (1948). — 15) Edmondson, H. A., Glass, S. J. and Soll, S. N.: *Proc. Soc. Exp. Biol. Med.*, N. Y., 42, 97 (1939). — 16) Morriore, T. G.: *Arch. Path.* 37, 39 (1944). — 17) Rather, L. J.: *Arch. int. Med.*, 80, 397 (1947). — 18) Lloyd, E. W. and Williams, R. H.: *Amer. J. Med.*, 4, 315 (1948). — 19) Bean, W. B.: *J. A. M. A.*, 121, 1412 (1943). — 20) Bean, W. B.: *Medicine*, 24, 243 (1945). — 21) Gilder, H. and Hoagland, C. L.: *Proc. Soc. Exp. Biol. Med. N. Y.*, 61, 62 (1946). — 22) Glass, S. J., Edmondson, H. A. and Soll, S. N.: *Endocrinology*, 27, 749 (1940). — 23) Zondek, B. and Black, R.: *J. clin. Endocrin.* 7, 519 (1947). — 24) Stealy, C. L. and Stimmel, B. F.: *J. clin. Endocrin.* 8, 67 (1948). — 25) Pincus, G., and Pearlman, W. H.: *Endocrinology*, 31, 507 (1942). — 26) Schiller, J.: *Endocrinology*, 36, 7 (1945). — 27) Hamburger, C.: *Nord. Med.*, 39, 1522 (1948 a); *Acta endocrinol.*, 1, 19 (1948 b). — 28) Forbes, A. P., Donaldson, E. C., Reifensstein, E. C. and Albright, F.: *J. clin. Endocrin.* 7, 264 (1947).

Aus der Medizinischen Klinik des Königl. Serafim-Krankenhauses, Stockholm.  
(Chefarzt: Prof. A. Kristenson.)

## Zur Frage des verlängerten QT.

Von

OLOF LJUNG.<sup>1</sup>

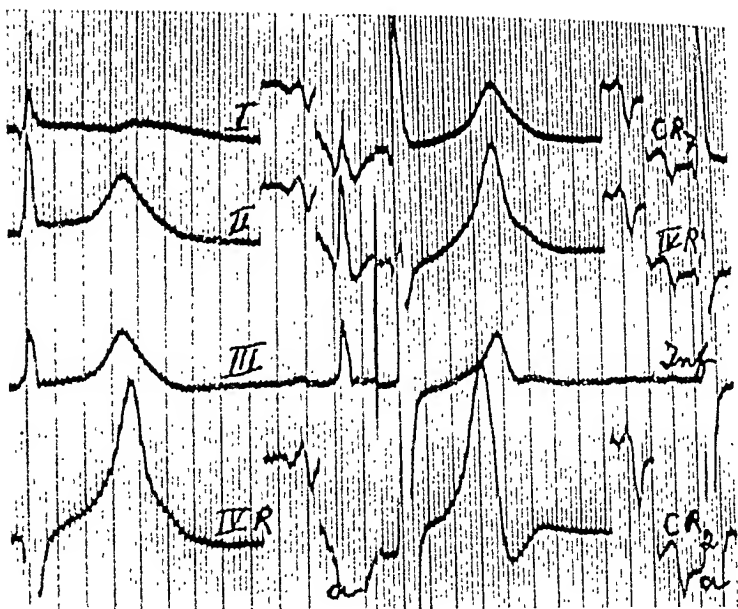
(Bei der Redaktion am 4. August 1949 eingegangen).

Das QT Intervall oder die elektrische Systole des Herzens ändert sich stark mit der Herzfrequenz. Um das Verhältnis des normalen QT zur Herzfrequenz zu berechnen, ist seit 1920 eine grosse Anzahl mehr oder weniger umständlicher Formeln vorgelegt worden. Ein Fehler der meisten Formeln ist unter anderem, dass sie allzu umständlich für den praktischen Gebrauch sind. Die vom Verfasser vorgeschlagene Formel  $QT = 0.2 \times RR + 0.18 \pm 0.04$  sek. gibt schnell einen zumindest für praktischen klinischen Gebrauch zufriedenstellenden Wert. Dabei ist das Interesse vor allem auf den oberen normalen Grenzwert gerichtet, also auf den Wert  $0.2 RR + 0.22$  sek. (Ljung 1948, 1949 b). Vorgeschlagene andere Formeln, Tabellen oder Normogramme, welche im Gebrauch schwieriger und zeitraubender sind, geben keine zuverlässigeren Werte.

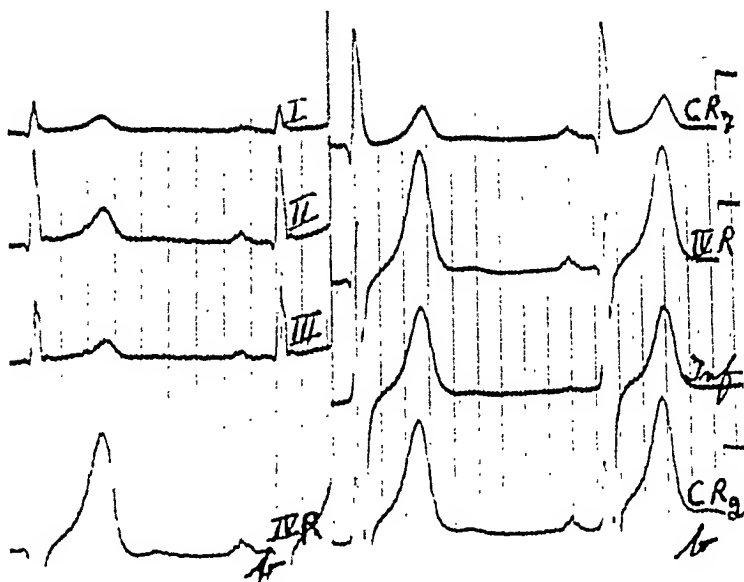
Der praktische klinische Wert der QT Beurteilung muss bisher als recht unbedeutend angesehen werden. Das verlängerte QT bei Hypokalzämie ist bekannt, und die Beachtung dieser Tatsache hat in nicht wenigen Fällen von Hypokalzämie zur richtigen Diagnose geführt, wo die Abwesenheit typischer Tetanie-Symptome die richtige Beurteilung des Krankheitsbildes verhindert hatte. Das Interesse für die Beurteilung des QT ist zeitweise etwas lebhafter gewesen. In U. S. A. hat das Interesse für diese Frage in der letzten Zeit anscheinend durch die Untersuchungen von Taran und Szilagyi (1947) zugenommen, welche dahin deuten, dass ein verlängertes QT das wichtigste elektrokardiographische Zeichen für rheumatische Carditis beim Kinde sei. Das Interesse für die QT Beurteilung scheint weiterhin gestiegen zu sein, nachdem Hegglin 1947 seine interessante Monographie über »Die Klinik der energetisch-dynamischen Herzinsuffizienz« herausgegeben hat. Hegglin findet bei einer Reihe von Krankheiten einerseits ein verlängertes QT Intervall, also eine verlängerte elektrische Systole, andererseits eine verkürzte mechanische Systole: er bezeichnet diesen Zustand als energetisch-dynamische Herzinsuffizienz. Diese kommt unter anderem bei Störungen im Mineral- und Kohlehydratstoffwechsel, bei Infektionen und toxischen Zuständen,

<sup>1</sup> Lasarettet Karlstad (Sweden).





1 a.



1 b.

Abb. 1. Fall 1: A. L. Mann, 32 Jahre alt, Haemorrhagia meningea. Abb. 1 a; 31. 7. 48 (am Tage nach Beginn der Erkrankung): T-Zacken auffällig breit. QT stark verlängert (um 0.21 sek.). In der Abl. Inferior ist QT jedoch nur um 0.05 sek. verlängert. b: am 27. 8. 48 beschwerdefrei. Die T-Zacken haben ein anderes Aussehen und QT ist nur um etwa 0.05 sek. in den meisten Abl. verlängert. Grosse U-Zacken sind wahrscheinlich die Ursache des »verlängerten QT«.

Leberinsuffizienz, Hypertonie, Haemorrhagia cerebri et meningea sowie beim Herzblock vor. Versucht man nun, Hegglin's Beobachtungen zu verwerten, so stösst man recht schnell auf ein Problem, welches meiner Meinung nach schwer zu lösen ist. Es zeigt sich nämlich, dass vor allem bei den oben angeführten krank-

haften Zuständen sehr oft grosse U-Zacken auftreten, welche oft eine Beurteilung von QT unmöglich machen, da die U-Zacken ganz oder teilweise mit den T-Zacken verschmelzen. Diese Ansichten sind früher in aller Kürze veröffentlicht worden (Ljung 1949 a).

Schon bei gesunden Menschen findet man manchmal nach körperlicher Anstrengung, dass die Messung von QT durch das Auftreten von U-Zacken erschwert

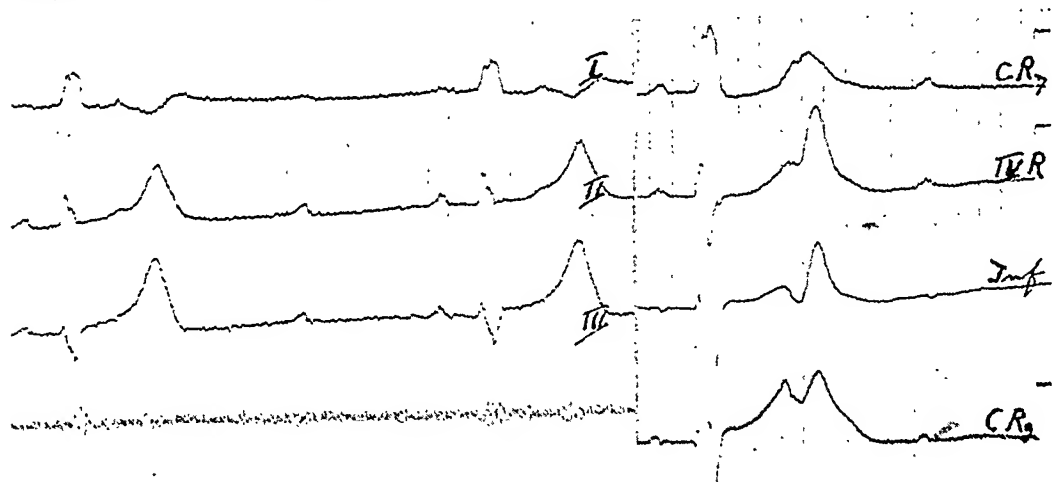


Abb. 2. Fall 2: K. L. Mann. 28 Jahre alt. Myocarditis acuta. QT ungefähr 0.80 sek. Die mechanische Systole um 0.16 sek. Hier müsste also eine ausgesprochene Dissoziation zwischen der elektrischen und mechanischen Systole vorliegen. Nach den Brustwandableitungen zu urteilen, ist jedoch die »Verlängerung von QT« durch das Auftreten riesiger U-Zacken verursacht.

wird, welche teilweise mit den T-Zacken verschmelzen. Fall 1 zeigt, wie bei einer frischen Haemorrhagia meningeum QT in den meisten Ableitungen stark verlängert ist, ungefähr um  $+0.21$  sek. (siehe Ljung 1948 und 1949 b). In der Brustwandableitung Inferior ist QT dagegen nur um  $+0.05$  sek. verlängert (Abb. 1 a). Zu dem Zeitpunkt, wo der Patient beschwerdefrei wird, ist QT in dieser Ableitung im grossen und ganzen fast unverändert und stimmt jetzt mit dem QT der anderen Ableitungen überein (Abb. 1 b). Man neigt in diesem Fall zu der Meinung, dass die »Verlängerung von QT« in Abb. 1 a abhängig ist von dem Auftreten grosser U-Zacken. Abb. 2 zeigt einen Fall von Myocarditis mit partiellem Block, 3:1 Block. Nach den Brustwandableitungen zu urteilen, ist man auch hier geneigt, das deutlich »verlängerte QT« mit dem Auftreten von sehr grossen U-Zacken zu erklären.

Fall 1. A. H. Mann. 32 Jahre alt. Am 30. 7. 1948 akut erkrankt mit Besinnungslosigkeit. Bei der Aufnahme Nackensteifigkeit. Sanguinolenter Liquor (Arteriographie zeigte später ein Aneurysma A. basilaris). Schon am 31. 7. bei Bewusstsein, unbedeutende Kopfschmerzen. Ekg: RR 1.15 sek. Auffällig breite T-Zacken in Abl. II, III, IV R und CR. QT in den meisten Ableitungen um 0.62 sek. also stark verlängert (nach Ljung um  $+0.21$  sek.). In der Ableitung Inferior beträgt jedoch QT nur 0.46 sek. oder  $+0.05$  sek. (Abb. 1 a). Ekg kurz vor der Entlassung am 27. 8: RR 0.95 sek., T-Zacken jetzt weniger breit. QT in mehreren Ableitungen um 0.42 sek. oder  $+0.05$  sek. (Abb. 1 b).

Fall 2. B. L. Mann. 28 Jahre alt. Akute Myokarditis. Stark mitgenommener Allgemeinzustand; RR ca. 2.1 sek. PQ: 0.22 sek. Partieller Block (3:1). Schenkelblock. »QT«

in mehreren Brustwandableitungen um 0.80 sek. Nach den Abl. IV R, Inf. und CR<sub>2</sub> zu urteilen, beruht jedoch das lange »QT« auf riesigen U-Zacken. Das wahre QT in Inf. ist 0.46 sek. Die mechanische Systole (gemessen von Q bis zum Beginn des 2. Tones) ist 0.44 sek. (Abb. 2).

Wenn man auch in diesen Fällen mit sicheren Schlussfolgerungen vorsichtig sein muss, so kann man doch Fälle aussuchen, bei denen man recht sicher sein kann, dass das »verlängerte QT« wirklich von dem Auftreten von U-Zacken abhängig ist. Dass die ausgesprochenste Verlängerung von QT sich bei den paroxysmalen Lähmungen der Muskulatur finden lässt, welche unter anderen durch eine Senkung des Serum-Kaliumgehaltes gekennzeichnet sind, ist ja schon seit langer Zeit bekannt. Auf mehreren der bei dieser Erkrankung veröffentlichten Ekg sieht man deutlich grosse U-Zacken. Jung und Jantz wiesen schon früher (1939) darauf hin, dass die breite, oft doppelgipflige T-Zacke, bei diesen Fällen evtl. durch eine grosse U-Welle bedingt sein kann, welche mit der T-Zacke verschmilzt.

Hegglin ist auch der Ansicht, dass Störungen im Kaliumstoffwechsel eine der wichtigsten Ursachen der »energetisch-dynamischen Herzinsuffizienz« sind, welche sich in der Regel mit einem gesenkten Serumkaliumwert zu erkennen geben. Bei Behandlung mit grossen Dosen Desoxicorticosteron erhält man oft eine deutliche Senkung des Serumkalium. In der letzten Zeit hat man mit Hilfe des Flammenphotometers zum ersten Male eine einfache und sichere Methode der Kaliumbestimmung. Fall 3 ist eine Patientin mit Anorexia nervosa: sie erhielt Desoxicorticosteron, so dass ihr Serumkalium bis auf Werte um 13 mg% sank. Keine subjektiven Beschwerden, die Pat. fühlt sich im Gegenteil frischer als vor der Behandlung. Nach den Extremitätenableitungen der Abb. 3 a zu urteilen, erscheint es einem als recht sicher, dass hier ein stark verlängertes QT vorliegt, aber wenn man die Brustwandableitungen bei der Beurteilung berücksichtigt, ist man eher geneigt, die »Verlängerung von QT« dem Auftreten einer grossen U-Welle zuzuschreiben. Die T-Zacken z. B. in Abl. II und III sind sicher nur eine U-Zacke. Kehrt später das Serumkalium nach Aussetzen der Behandlung zu normalen Werten zurück, so treten die T-Zacken mehr und mehr in Erscheinung und die U-Zacken verschwinden. (Die Bestimmungen des Serumkalium mit dem Flammenphotometer wurden durch das Entgegenkommen der Doktoren R. Luft und B. Sjögren ermöglicht.)

*Fall 3.* G. E. Fräulein. 34 Jahre alt. Tbc. pulmonum mit rechtsseitigen Pneumothorax. Keine Bazillen im Sputum. Aufgenommen wegen typischer Anorexia nervosa. Nach 14 tägiger Behandlung mit täglich 10 g NaCl und 20 mg Desoxicorticosteron (Percorten, Ciba) subjektiv besser, frischer. Blutdrucksteigerung systolisch von 100 mm Hg auf Werte um 140 mm Hg. Senkung des Serumkalium bis 12 mg%. Ekg am 5. 2. 1949 (Serumkalium 13.4 mg%): RR 1.15 sek. Nach den Abl. II und III zu urteilen, würde QT 0.60 sek. oder + 0.19 sek. betragen und somit stark verlängert sein (Abb. 3 a). Angesichts der Brustwandableitungen kann man jedoch argwöhnen, dass die Verlängerung von »QT« in der Hauptsache durch das Entstehen einer grossen U-Zacke bedingt ist. Diese Annahme bestätigt auch der Verlauf, welcher dahin deutet, dass die sichtbare positive Zacke in den Abl. II und III der Abb. 3 a eine U-Zacke war. Schon am 11. 2. beginnt die T-Zacke, die Überhand über die U-Zacke zu gewinnen (Abb. 3 b). Am 25. 2. ist das Serumkalium mit 18.2 mg% normal. Die U-Zacke ist jetzt ganz verschwunden (Abb. 3 d.)

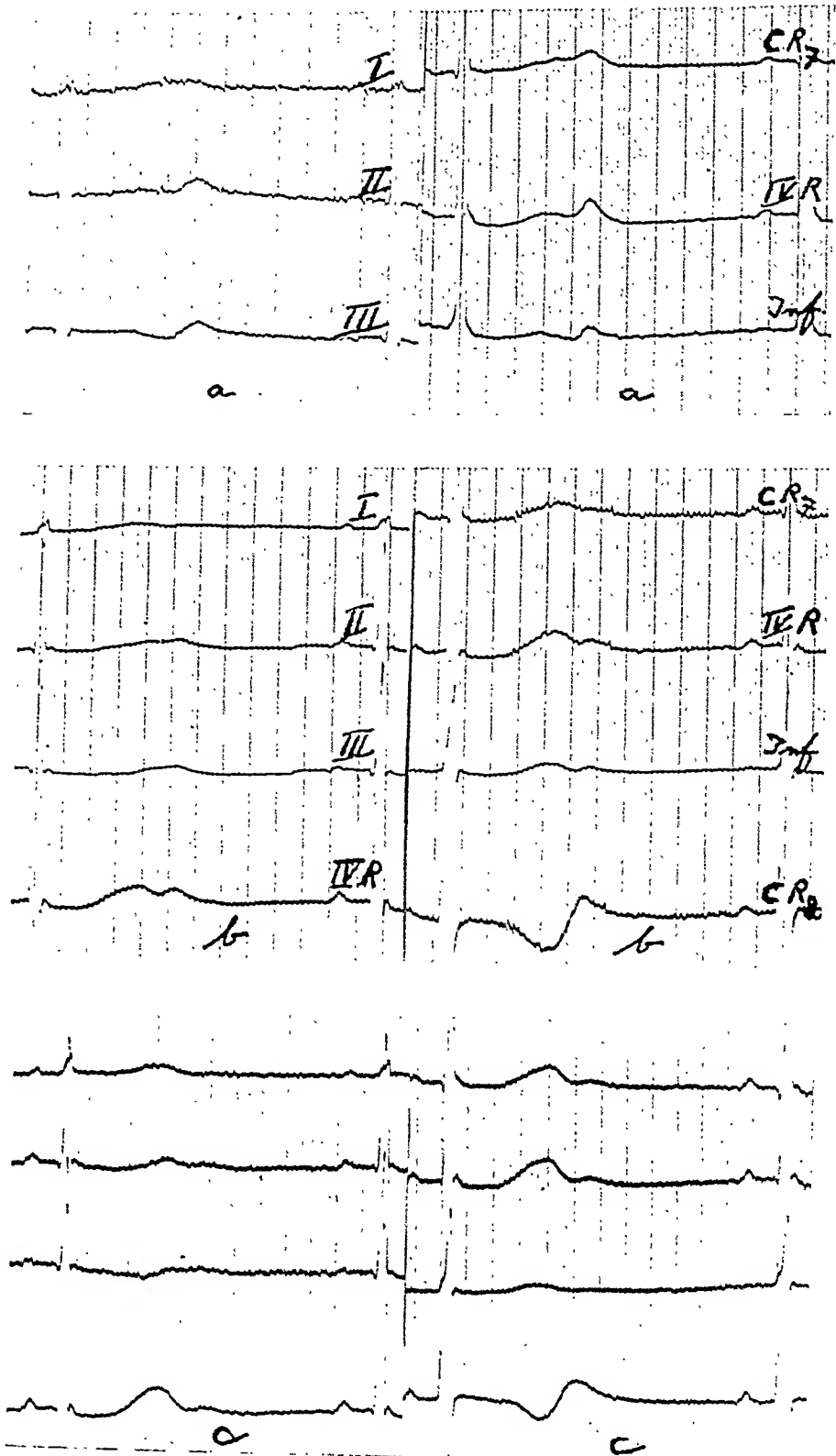


Abb. 3. Fall 3: G. E. Fräulein, 33 Jahre alt. Anorexia nervosa. Nach Kochsalz und Desoxicorticosteron Hypokaliämie. Abb. 3 a: am 5. 2. 49 (Serumkalium 13.4 mg%) QT in Abl. II und III um + 0.19 sek. Brustwandableitungen und der spätere Verlauf zeigen, dass die »Verlängerung von QT« ziemlich sicher durch eine grosse U-Zacke verursacht wird: b: 11. 2 und c: 16. 2. Die T-Zacken treten mehr und mehr in den Vordergrund; gleichzeitig werden die U-Zacken kleiner. d: 25. 2. 49: Serumkalium normal (18.2 mg%); die U-Zacken jetzt ganz verschwunden.

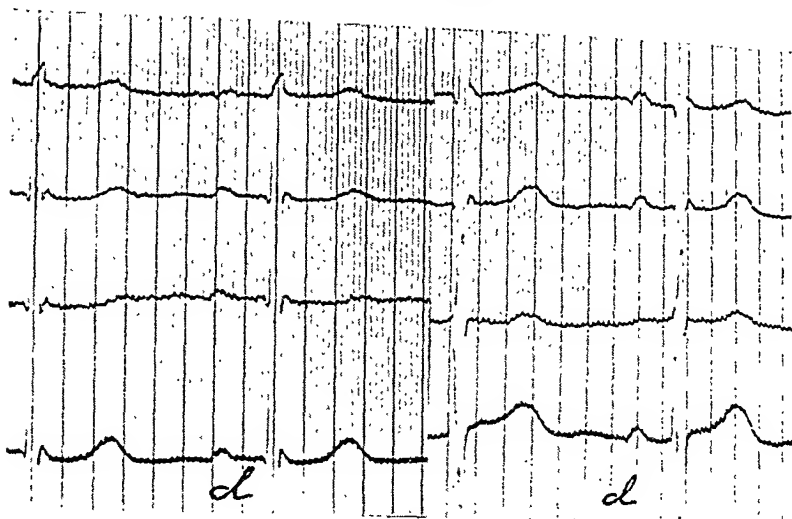


Abb. 3 d.

Fall 4 ist ein leichter Erschöpfungszustand nach akuter Hepatitis; auch hier wurde Desoxicorticosteron bis zu einer Senkung des Serumkalium bis auf Werte um 13 mg% gegeben. Auch hier sieht man deutlich, wie die T-Zacken in mehreren Ableitungen gesenkt werden und U-Zacken auftreten. In Abl. CR, z. B. vermisst man die T-Zacke völlig und die U-Zacke würde man hier leicht als eine T-Zacke auslegen können.

*Fall 4.* I. L. Frau. 36 Jahre alt. Mai 1948 akute Hepatitis mit verzögertem Verlauf. Seitdem müde. Leberfunktionsprüfungen vor diesem Untersuchungen: normal. Genau wie Fall 3 erhielt die Pat. täglich 10 g NaCl und 20–25 mg Percorten und zwar 14 Tage lang. Mässiger Blutdruckanstieg und während der letzten Behandlungstage leichter Kopfschmerz und angedeutetes Gesichtsoedem. Sonst keine subjektiven Beschwerden. Ekg am 5. 2. 49 (Serumkalium 13.3 mg%): RR 1.10 sek. In den Abl. I und Inferior beträgt QT um 0.43 sek. oder  $\pm 0.03$  sek., in den übrigen erhält man »QT«-Werte bis zu 0.64 sek. oder  $\pm 0.24$  sek., welche durch das Auftreten von U-Zacken bedingt sind; diese können in CR<sub>2</sub> leicht mit T-Zacken verwechselt werden (Abb. 4 a). Am 1.3. sind bei normalem Serumkalium von 17.4 mg% die U-Zacken ganz verschwunden. RR 0.95 sek. und QT 0.38 oder  $\pm 0.01$  sek. (Abb. 4 e). Rechnet man die U-Zacken nicht mit, würde also QT in a und c ziemlich unverändert sein.

Durch oft wiederholte Ekg und synchrone Registrierung mehrerer verschiedener Ableitungen findet man in vielen Fällen, dass das, was leicht als ausgesprochene QT-Verlängerung gedeutet werden kann, völlig oder zumindest zum grössten Teil auf der Entstehung grosser U-Zacken zu beruhen scheint. Abb. 5 zeigt grobschematisch einige der verschiedenen Variationen, die man hierbei erhalten kann. Auf einem vereinzelt Ekg zur Zeit der stärksten Störung kann es schwer oder unmöglich sein, U-Zacken zu erkennen, besonders wenn man nur mit Extremitätenableitungen oder irgend einer einzelnen Brustwandableitung arbeitet. Wiederholte Ekg bei den Fällen, wo die Störung zurückgeht, geben jedoch einen deutlichen Bescheid.

Was die U-Zacken verursacht, ist nicht sicher bekannt. Einige spätere Unter-

sucher schliessen sich der Ansicht Vesa's (1939) an, dass die U-Zacke durch einen Aktionsstrom von der Abgangsstelle von Aorta und A. pulmonalis entsteht. Nahum und Hoff (1939) sind dagegen der Meinung, dass die U-Zacke einen Teil des Ventrikelkomplexes ausmacht und daher als zu der elektrischen Systole gehörig ge-

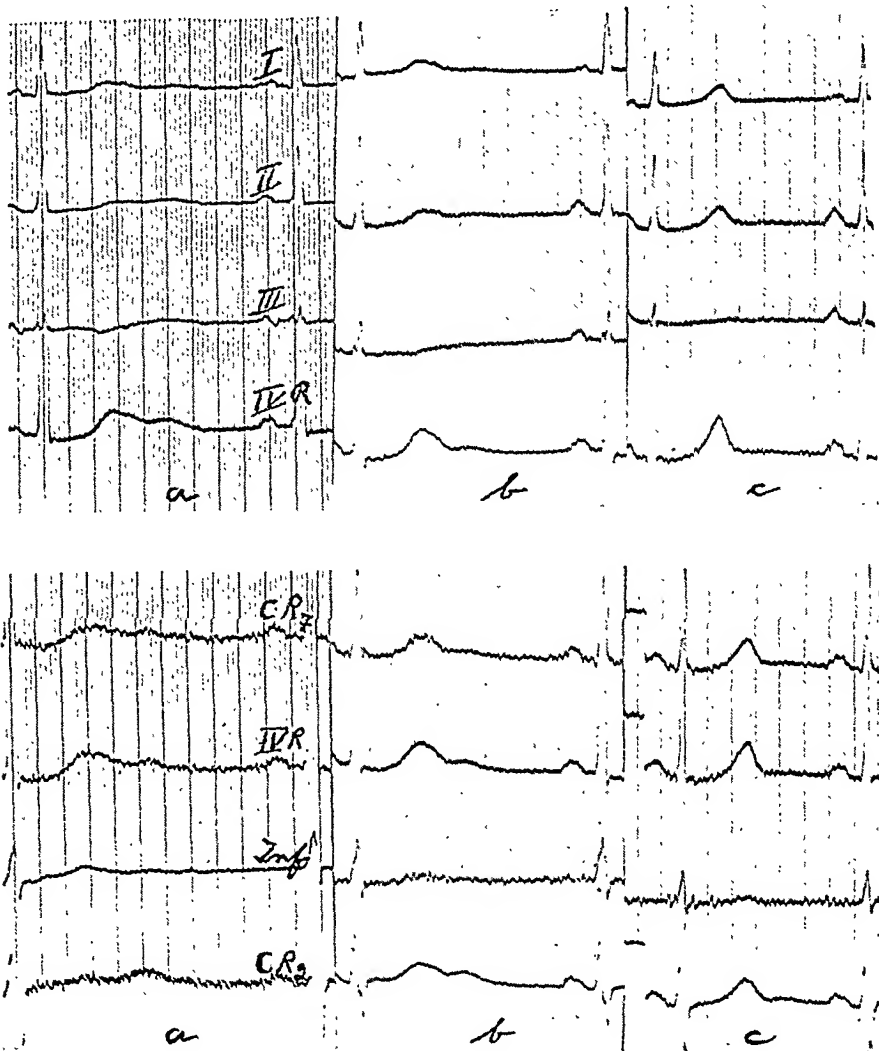


Abb. 4. Fall 4: I. L. Weib, 36 Jahre alt. Erschöpfungszustand nach akuter Hepatitis. Nach Kochsalz und Desoxicorticosteron Hypokaliämie. Abb. 4 a: 5. 2. 49 (Serumkalium 13.3 mg%). QT in Abl. I und Inferior um + 0.03 sek., aber in den übrigen Abl. »QT« um + 0.24 sek., also stark verlängert. »QT« Verlängerung bedingt durch grosse U-Zacken. In CR, kann die U-Zacke leicht mit einer T-Zacke verwechselt werden. b: 9. 2. c: 1. 3. 49 (Serumkalium 17.4 mg%). Die U-Zacken jetzt verschwunden.

rechnet werden sollte. Will man sich der letzten Ansicht anschliessen, so würde es vielleicht korrekt sein, die elektrische Systole mit QU anstatt mit QT zu definieren. Ohne hier näher auf dieses Problem eingehen zu wollen, scheint es jedoch inkonsequent zu sein, in QT nur die U-Zacken einzubeziehen, welche ganz oder teilweise mit den T-Zacken verschmelzen, während man die U-Zacken nicht mit einbezieht, welche deutlicher von den T-Zacken abgegrenzt sind (Variation 2). Wie aus mehre-

ren Ekg hervorzugehen scheint, welche von Hegglin und anderen Untersuchern veröffentlicht wurden, wird jedoch eine derartige Beurteilung angewandt. Wenn die Variation 2 in z. B. Variation 3 übergeht, erhält man mit dieser Beurteilung eine »sprunghafte« Verlängerung von QT beispielsweise 0.15 sek. Ähnliche Kritik der Beurteilung von QT ist früher bei einem Teil der hier erwähnten Zustände mit

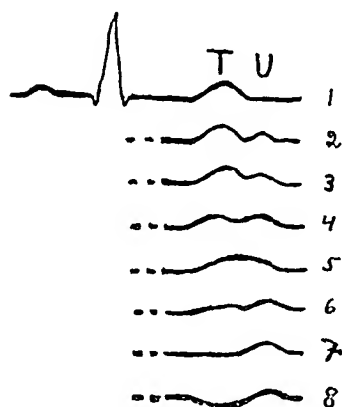


Abb. 5. Zeigt schematisch verschiedene Variationen der T- und U-Zacken, von denen die Variationen 3—8 Schwierigkeiten bei der Messung von QT machen können.

verlängertem QT veröffentlicht worden. Grut und Lund (1939) haben hervorgehoben, dass Hadorn (1936) und Hegglin (1938) bei der Beurteilung von Ekg bei Hypoglykämie die U-Zacken in QT einbeziehen. Mehrere andere Verfasser haben darauf hingewiesen, dass das Auftreten einer U-Zacke oft zu Schwierigkeiten bei der Bestimmung von QT führt. Diese Anmerkungen sind jedoch nicht näher präzisiert und offensichtlich gering beachtet worden.

Ob und inwieweit diese Anmerkungen ebenfalls die QT-Beurteilung bei Hypokalzämie betreffen, ist schwerlich sicher zu beantworten, dürfte aber wohl kaum der Fall sein. Man findet hierbei selten eine breite T-Zacke, und QT wird ganz allmählich länger parallel zu den fallenden Kalziumwerten. Bei Untersuchung von über 30 Fällen mit ausgesprochener,

zumeist postoperativer, Hypokalzämie habe ich nur bei einer Gelegenheit bei einem der Fälle eine sprunghafte Verlängerung gefunden, welche man als durch das Auftreten einer U-Zacke bedingt deuten könnte.

Zusammenfassend kann gesagt werden, dass man bei einem Teil der Zustände, welche als »energetisch-dynamische Herzinsuffizienz« beschrieben sind, nicht selten durch nähere Analys der Ekg finden kann, dass die Verlängerung von QT ganz oder zumindest hauptsächlich durch das Auftreten einer U-Zacke bedingt ist, welche ganz oder teilweise mit der T-Zacke verschmilzt oder bei Abwesenheit einer deutlichen T-Zacke als T-Zacke gedeutet wird. Wenn man weiterhin versuchen will, in dieser Richtung weiterzukommen, so muss man eine konsequentere Beurteilung anwenden, und es müssen klare Definitionen der Begriffe QT und elektrische Systole aufgestellt werden.

## Summary.

### *Prolongation of the Q-T Interval.*

Report of a case of meningeal haemorrhage and of a case of acute myocarditis with partial auriculo-ventricular heart-block. In both cases the »marked prolongation of the Q-T interval« was, if not entirely, at all events partly due to the appearance of a U-wave. A decrease in the serum potassium to about 13 mg % following the administration of desoxycorticosterone was observed in a case of

subacute hepatitis and a case of anorexia nervosa. The electrocardiograms taken at that time showed large U-waves while the amplitude of the T-waves was reduced. This may lead to misinterpreting the Q-U interval as being a markedly prolonged Q-T interval.

In a fair number of cases described in the literature the prolongation of the Q-T interval observed in various pathological conditions was probably essentially due to the appearance of a U-wave. In many cases it will therefore be necessary to make several tracings, using several chest leads to clarify this problem.

#### Literaturverzeichnis.

- Grut, A. und Lund, M.: Nord. med. 4: 3805, 1939. — Hadorn, W.: Ztschr. f. klin. Med. 130: 643, 1936. — Hegglin, R.: Cardiologia 2: 170, 1938. — Hegglin, R.: Die Klinik der energetisch-dynamischen Herzinsuffizienz. Bibliotheca Cardiologica, Fasc. II, 1947. — Jung, R. und Jantz, H.: Verhandl. d. deutsch. Gesellsch. f. Kreislaufforsch. 12: 217, 1939. — Ljung, O.: Svenska läk. tidn. 45: 2125, 1948. — Ljung, O.: Ibid. 46: 548, 1949 a. — Ljung, O.: Acta med. Scandinav. 134: 79, 1949 b. — Nahum, L. H. und Hoff, H. E.: Am. Heart J. 17: 585, 1939. — Taran, L. und Szilagyi, N.: Am. Heart J. 33: 14, 1947. — Vesa, A.: Acta Soc. Med. Fenn. »Duodecim» Ser. B. 26, Fasc. 13, 1938.
-



From the Medical Department B, Frederiksberg Hospital, Copenhagen.  
(Director: N. R. Christoffersen, M. D.)

## The Examination of Isolated Serum Proteins by the Mercuric Chloride and Thymol Reactions.<sup>1</sup>

By

K. ALBERTSEN, N. R. CHRISTOFFERSEN and F. HEINTZELMANN.

(Submitted for publication May 20, 1949.)

Owing to the difficulties in the fractionation of serum proteins and particularly of globulin, such estimations have not so far been used for routine examinations in the medical clinic. A number of simple laboratory tests have been developed instead (formol-gel, Takata-Ara, colloidal-gold precipitation, cephalin-cholesterol, mercuric chloride and thymol tests). All these tests depend on protein precipitation. Various attempts have been made to demonstrate that in the different tests the precipitation is due to some definite protein fractions in the serum. Evidence for this has been produced, but this question needs further examination.

In this paper we hope to contribute towards the solution of this problem by investigating the protein fractions which are precipitated in the mercuric chloride test and in the thymol test. We believe that these tests are particularly useful because the results can be recorded as simple quantitative values.

Through the courtesy of the State Serum Institute we obtained pure isolated protein fractions and we record our thanks to their Director, Dr. J. Ørskov, and to the Departmental Director, Dr. Albert Hansen, for their valuable help. The isolated serum proteins — albumin,  $\alpha$ -,  $\beta$ - and  $\gamma$ -globulins — were prepared in the State Serum Institute by fractionation with alcohol by Cohn's (5) method from the blood of patients with hepatitis and from controls (mostly patients with hypertension).

Our experiments were carried out with these protein fractions dissolved in physiological saline, with a pH of about 7.0. Some experiments have been made with protein fractions dissolved in serum.

---

<sup>1</sup> Read at the 21st Scandinavian Congress for Internal Medicine, Copenhagen, 1948.

### Mercuric Chloride Titration.

So far only few papers have discussed this problem. Investigations have shown that the mercuric chloride reaction in serum (Takata-Ara reaction, mercuric chloride titration) depends partly on the amount of globulin and partly on the albumin-globulin-ratio and the reaction becomes positive only when this ratio is less than 1 (Staub and Jezler (12), Ucko (14), Bjørneboe (2)), presumably because albumin inhibits the precipitation. Ucko thought that albumin from the sera of healthy subjects exerted a stronger inhibition than the albumin from Takata-Ara-positive sera.

Gros (6), de Vries (15), and Balint and Balint (1) believed that pseudoglobulin I and particularly euglobulin are precipitated by mercuric chloride. Of all the fractions prepared by the salting method previously employed, euglobulin practically corresponds to  $\alpha$ - and  $\beta$ - globulins, while pseudoglobulins I and II approximately correspond to  $\gamma$ -globulin.

Electrophoretic studies (Wuhrmann (16)) indicate that the reaction is due to the presence of  $\beta$ - and  $\gamma$ -globulins, while the cephalin-cholesterol reaction and the colloidal-gold reaction are due to  $\gamma$ -globulin (Kabat et al. (7), Moore et al. (10)).

### Investigations.

We have made studies with a modification of the Takata-Ara test introduced by Gros and later modified by Stolte (13) (Christoffersen and Raagaard (3)):

A 0.1 % mercuric chloride solution is added drop by drop to 1 ml of serum until a turbidity appears which remains for 1/2 min., and through which ordinary print cannot be read. In these experiments we have used 1 ml of the protein solutions we wished to investigate instead of the serum.

The titration value is expressed in ml of mercuric chloride solution added. This means that the lower the recorded value, the more protein which may be precipitated is present in the solution examined.

In our experiments, titration values over 10 are regarded as absence of precipitation.

A brief account of our results follows:

*Serum albumin:* Solutions of albumin in saline in various concentrations up to 10 % gave no precipitate even when 10 ml mercuric chloride solution were added.

*$\alpha$ -globulin solutions* were not precipitated by mercuric chloride, whether dissolved in saline with or without albumin or in normal human serum, as the titre remained constant after the addition of  $\alpha$ -globulin. Some experiments, however, indicate that  $\alpha$ -globulin is not altogether without influence on the result if present in solutions together with  $\gamma$ -globulin, but our experiments are not sufficient to permit definite conclusion. The available  $\alpha$ -globulin did not allow us to make more experiments.

*$\gamma$ -globulin solutions,* on the other hand, gave a distinct precipitate in all the experiments as is shown in Table I giving the titration values for different con-

centrations of  $\gamma$ -globulin solutions derived from controls as well as from patients with hepatitis.

Table I shows that smaller concentrations of  $\gamma$ -globulin require more mercuric chloride. Concentrations of less than 0.5 % do not produce a precipitate even when 10 ml mercuric chloride is added. Other experiments showed that when the  $\gamma$ -glob-

Table I.

*Titration of  $\gamma$ -globulin solutions in saline with mercuric chloride.*

$\gamma$ -globulin %	In ml of mercuric chloride	
	hepatitis	control
5 .....	0.38	0.33
4 .....	0.50	0.33
3 .....	0.50	0.38
2 .....	0.80	0.48
1 .....	1.53	1.08
0.5 .....	2.43	2.18
0.25 .....	10	10

ulin concentration was higher than 5 %, the titre remained constant. A 10 % solution did not give a lower titre than a 5 % solution, therefore the reaction reaches its maximum already when the  $\gamma$ -globulin concentration is about 5 %. For solutions of less than 5 %, however, it is true that the higher the  $\gamma$ -globulin concentration the lower is the titre.

Table I also shows that the titre is about the same for  $\gamma$ -globulin whether it comes from patients with hepatitis or from controls. Normal  $\gamma$ -globulin always gives a slightly stronger reaction.

When  $\gamma$ -globulin is dissolved in *normal serum* the precipitation is also stronger than with serum alone, and the titre likewise decreases with the increasing globulin concentration. The values, however, do not reach such low levels as in titration in saline, perhaps because of inhibitory substances in the serum.

When dissolved with albumin,  $\gamma$ -globulin is also precipitated by mercuric chloride, but the reaction becomes much weaker, as is shown in Table II.

Table II.

*Titration of  $\gamma$ -globulin by mercuric chloride, with and without addition of albumin (in varying amounts) from patients with hepatitis and from controls.*

$\gamma$ -globulin %	In ml of mercuric chloride				
	globulin without albumin	with albumin 2.5 %		with albumin 5 %	
		from hepatitis	from control	from hepatitis	from control
5 .....	0.33	0.63	0.83	1.08	1.08
3 .....	0.38	0.90	1.05	1.23	1.45
2 .....	0.48	1.15	1.58	1.65	2.23
1 .....	1.08	1.93	3.13	2.70	5.28

Table II shows the titration values obtained for solutions of normal  $\gamma$ -globulin in various concentrations, alone and with albumin (2.5 or 5 %), both from controls and from patients with hepatitis. The titre for  $\gamma$ -globulin dissolved in saline is lower than for the same concentration of globulin dissolved with albumin. It is lower in solutions with 2.5 % albumin than in solutions with 5 % albumin and is also lower in solutions of globulin together with albumin from cases of hepatitis than in solutions of globulin together with normal albumin.

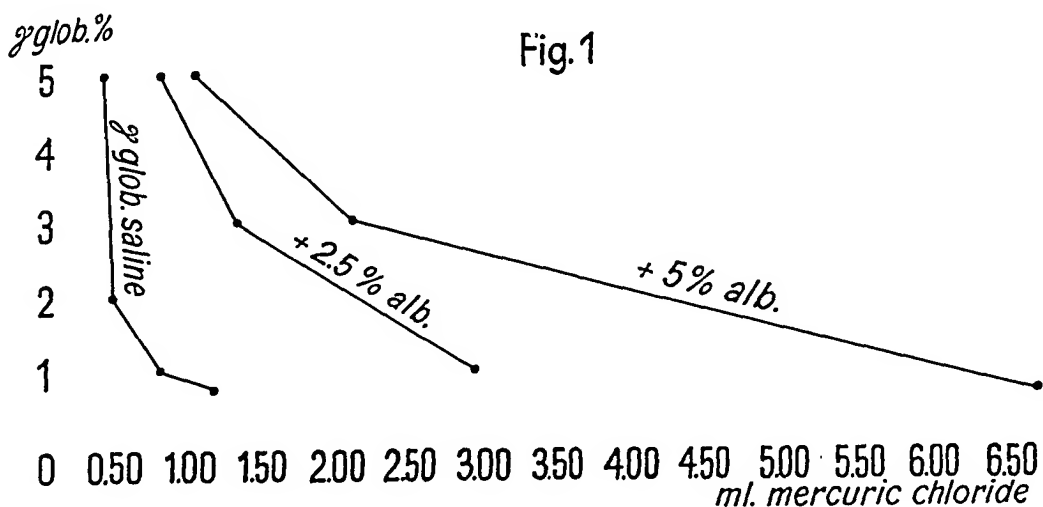


Fig. 1. Mercuric chloride titration of  $\gamma$ -globulin solutions with or without albumin (2.5 and 5 % respectively).

This indicates that the titre does not depend on the  $\gamma$ -globulin concentration alone, but also on the amount of albumin added and on the source of this albumin (from controls or from patients with hepatitis). This is shown in Fig. 1, which illustrates that albumin has an inhibitory effect on the precipitation of  $\gamma$ -globulin by mercuric chloride: thus the more albumin there is in the solution, the more mercuric chloride is required for the precipitation.

Experiments with  $\beta$ -globulin were associated with considerable difficulties. It proved to be very difficult to prepare solutions after the  $\beta$ -globulin had been precipitated, whether we used saline in various concentrations, several albumin solutions or serum.

Therefore other methods were tried.

After the removal of albumin and  $\alpha$ -globulin from the plasma,  $\beta$ - and  $\gamma$ -globulins remained in the solutions in *about equal parts* and by continued fractionation and precipitation we obtained separately about equal amounts of  $\beta$ -globulin and  $\gamma$ -globulin (by weight). The  $\beta$ -fraction thus isolated could not be dissolved, but the  $\gamma$ -fraction dissolved readily. When  $\beta$ - and  $\gamma$ -globulins are prepared together in dry form, a mixture is easily dissolved again.

Therefore we compared the mercuric chloride precipitation of such  $\beta$ - and  $\gamma$ -solutions, with solutions of pure  $\gamma$ -globulin in the same concentrations, and we were thus able to draw conclusions about the influence of  $\beta$ -globulin on the result of the re-

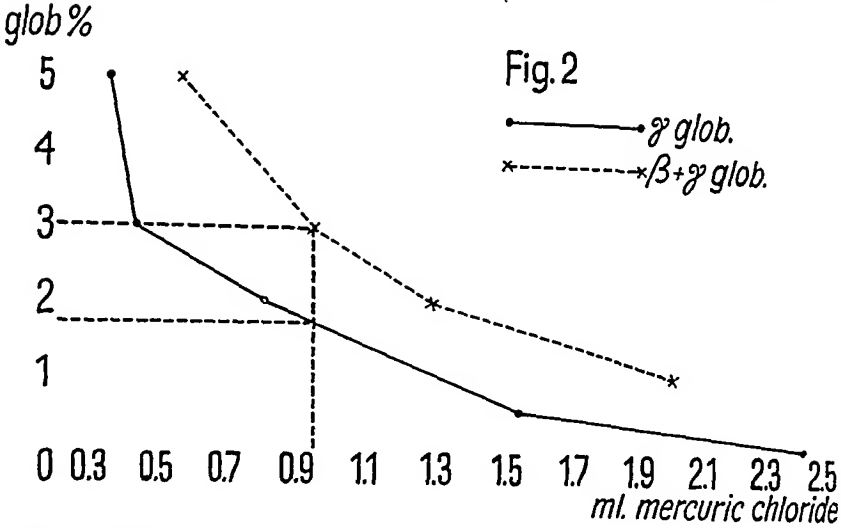


Fig. 2. Mercuric chloride titration of  $\gamma$ -globulin and  $\beta$ - and  $\gamma$ -globulin solutions.

actions. The reaction in this method, however, is weaker, as shown in Table III and the titre is much higher in the  $\beta$ - and  $\gamma$ -globulin solutions than in the solution of  $\gamma$ -globulin alone and indicates that the  $\beta$ - and  $\gamma$ -globulin solution contains a smaller amount of globulin which can be precipitated.

It must be remembered that in the  $\beta$ - and  $\gamma$ -mixture the  $\gamma$ -globulin only amounts to about half of the total amount of globulin. A  $\beta$ - and  $\gamma$ -globulin solution of a certain concentration gives about the same titre as a pure  $\gamma$ -globulin solution of half the concentration. We have tried to illustrate this in Fig. 2 where the titration curves for  $\gamma$ -globulin and  $\beta$ - and  $\gamma$ -globulin solutions (from normal blood) are shown.

The stippled line shows that a  $\beta$ - and  $\gamma$ -globulin solution of 3 % gives a titre of 0.95, and the same titre is obtained for a  $\gamma$ -globulin concentration of about 1.70 %.

Table III.

Titration with mercuric chloride of  $\beta$ - and  $\gamma$ -globulins in saline, with and without albumin from controls and from patients with hepatitis. For comparison, the first column gives the titres for a pure  $\gamma$ -globulin solution. All the globulins come from patients with hepatitis.

Hepatitis globulin concentration %	In ml of mercuric chloride solution					
	$\gamma$ -globulin from hepa- titis with- out albu- min	$\beta$ - and $\gamma$ -globulin from hepatitis				
		without albumin	with albumin 2.5 %		with albumin 5 %	
			from hepatitis	from controls	from hepatitis	from controls
5 .....	0.38	0.58	turbid	1.00	1.00	1.75
3 .....	0.50	0.95	0.98	1.40	1.45	1.35
2 .....	0.80	1.28	1.38	2.25	2.03	2.63
1 .....	1.53	2.00	2.55	4.13	3.63	5.35
0.5 .....	2.43	2.63	—	—	—	—

The addition of albumin has the same influence on the precipitation of  $\beta$ - and  $\gamma$ -globulins by mercuric chloride as was observed in the experiments with pure  $\gamma$ -globulin. The titre increases with increasing amounts of albumin, and it becomes even higher and the reaction weaker when the albumin is derived from normal blood instead of blood from patients with hepatitis. This is a constant phenomenon, as shown by the example recorded in Table III; the titre rises steadily in the columns from the left to the right: the titre is higher for  $\beta$ - and  $\gamma$ -globulin than for  $\gamma$ -globulin alone, higher after the addition of normal albumin than of albumin from cases of hepatitis, and higher after the addition of 5 % albumin than of a 2.5 % solution.

### Discussion.

We believe that we are justified to draw the conclusion that of all the serum proteins it is the  $\gamma$ -globulin — and this alone — which is precipitated by mercuric chloride. When the  $\beta$ - and  $\gamma$ -globulin solutions give a weaker reaction than a pure globulin solution, it may be argued that this might be due to an inhibitory effect of  $\beta$ -globulin, but because the reaction on the whole follows the pure  $\gamma$ -globulin content, it is suggested that the  $\beta$ -globulin content does not influence the reaction.

We have demonstrated that the precipitation of  $\gamma$ -globulin by mercuric chloride is inhibited by the addition of albumin, and this inhibition increases with increasing amounts of albumin. Albumin from normal blood has a stronger inhibitory effect than albumin from blood of cases of hepatitis.

These conclusions are based on an extensive investigation in which all the experiments have given the same results. The tables presented merely record examples of such experiments.

Our results are not really comparable with those from experimental studies where the serum proteins were obtained by salting, as the latter are not identical with the  $\alpha$ -,  $\beta$ - and  $\gamma$ -globulins. Wuhrmann and Wunderly (16), using electrophoresis in their investigations, believe that mercuric chloride precipitates both  $\beta$ - and  $\gamma$ -globulins, but our experiments indicate that  $\beta$ -globulin is not precipitated by mercuric chloride.

Ueko (14) examined sera by the Takata-Ara test and found that addition of albumin inhibited this reaction, and that albumin from normal blood was more inhibitory than albumin from Takata-positive sera. The result of our experiments with isolated protein in saline solutions lends support to this view.

### Thymol Test.

The thymol test was introduced by MacLagan (9) who thought that the positive result of the reaction depended on the  $\gamma$ -globulin content of the serum. Recant *et al.* (11), on the other hand, thought that the precipitation was due to a globulin component combined with lipid, and claimed that  $\gamma$ -globulin solutions gave no precipitate with thymol.

From experiments with electrophoresis Cohen and Thompson (4) found the reaction to be due to  $\beta$ -globulin exclusively. On the other hand, Kunkel and Hoagland (8) found that the reaction depended upon lipoids in the serum as well as globulins and that both  $\beta$ - and  $\gamma$ -globulins influenced the reaction. They found that the reaction was inhibited when the albumin content of the serum was increased to more than twice the initial content.

### Investigations.

The thymol test was carried out as directed by Maclagan, and the results were read by means of a Pulfrich photometer. The strength of the reaction is given in Maclagan units.

Our results were as follows:

*Serum albumin does not react with thymol even in 10 % solution.*

*$\alpha$ -globulin does not react with thymol, either in pure saline solution or with the addition of albumin of up to 5 %.*

*$\gamma$ -globulin dissolved in saline is precipitated promptly by thymol, in gradually increasing degree with the increasing concentration, the titre being directly proportional to the concentration. All our experiments gave the same result. Two examples are recorded in Table IV.*

As it was found impracticable to prepare solutions of pure  $\beta$ -globulin, we used the same procedure in the thymol tests as in the mercuric chloride tests, *e. g.*, comparison of solutions of pure  $\gamma$ -globulin and of  $\beta$ - and  $\gamma$ -globulins.

*Solutions of  $\beta$ - and  $\gamma$ -globulins in saline reacted strongly with thymol in all our experiments. The reaction was much stronger than for solutions of pure  $\gamma$ -globulin: this titre also increases with increasing concentration, almost in direct proportion to the concentration.*

Table IV shows that  $\gamma$ -globulin as well as  $\beta$ - and  $\gamma$ -globulins from normal subjects are precipitated somewhat more readily than are the same fractions derived from patients with hepatitis.

The relation between the precipitation of  $\gamma$ -globulin and of  $\beta$ - and  $\gamma$ -globulins by thymol is shown in Fig. 3, in which titration curves for solutions of these frac-

Table IV.

*Thymol titration of  $\gamma$ - and  $\beta + \gamma$ -globulins from patients with hepatitis and from controls.*

Total globulin concentration %	Thymol titre (Maclagan units)			
	$\gamma$ -globulin controls	$\gamma$ -globulin hepatitis	$\beta + \gamma$ -globulins controls	$\beta + \gamma$ -globulins hepatitis
10 .....		8.6		21.2
5 .....	9.9	4.5	13.2	10.6
4 .....	7.0	—	11.6	—
3 .....	5.0	—	9.2	—
2 .....	3.3	1.3	4.7	3.9
1 .....	1.1	1.0	2.4	2.0
0.5 .....	0	0.6	0.2	1.1
0.25 .....	0		0.2	





Table V.

*Thymol titration of  $\gamma$ -globulin with and without albumin (2.5 % or 5 %) from patients with hepatitis and from controls.*

$\gamma$ -globulins %	Thymol titre (MacLagan units)				
	$\gamma$ -globulins without albumin	with albumin 2.5 %		with albumin 5 %	
		from hepatitis	from controls	from hepatitis	from controls
5 .....	9.9	8.6	8.1	8.3	7.9
3 .....	5.0	4.7	4.5	4.4	4.5
2 .....	3.3	2.9	3.4	2.9	2.8
1 .....	1.1	1.1	1.1	1.0	0.6

We have examined the thymol precipitation of globulin dissolved in normal serum, and found a considerably higher titre than observed in solutions of the same globulin in saline (Table VI).

Table VI.

*Thymol titration of  $\gamma$ -globulin and  $\beta + \gamma$ -globulin from patients with hepatitis — dissolved in human serum.*

Concentration in %	Thymol titre (MacLagan units)	
	$\gamma$ -globulin	$\beta + \gamma$ -globulin
10 .....	42.6	33.4
5 .....	25.7	19.7
3 .....	19.2	12.3
1 .....	4.1	3.0
0.5 .....	1.5	1.4
0 .....	0.6	0.6

As shown in Table VI we found the peculiar fact that  $\gamma$ -globulin gave the highest titre and the strongest precipitation. The titre of  $\beta$ - and  $\gamma$ -globulins is about 50 % higher when the globulins are dissolved in serum than when dissolved in saline, while the titre of  $\gamma$ -globulin is about 300 % higher. We are unable so far to explain this finding, and at present we merely wish to put forward the hypothesis that it may be due to various substances (lipoids) in the serum.

## Discussion.

We have found that while albumin and  $\alpha$ -globulin are not precipitated by thymol it causes a strong precipitation of  $\gamma$ -globulin as well as  $\beta$ - and  $\gamma$ -globulins. This reaction is weaker for the fractions derived from patients with hepatitis than from controls, and the precipitation appears to be directly proportional to the globulin concentration. As  $\beta$ - and  $\gamma$ -globulins are precipitated more strongly than  $\gamma$ -globulin and as the  $\beta$ - and  $\gamma$ -fraction contains about equal amounts of  $\beta$ - and  $\gamma$ -globulins, this indicates that unless  $\beta$ -globulin promotes the precipitation of  $\gamma$ -glob-

ulin,  $\beta$ -globulin is precipitated more strongly than  $\gamma$ -globulin (up to 3 times as strongly).

The following 4 theories have been formulated about this test:

- 1) The precipitation is due to  $\gamma$ -globulin (MacLagan),
- 2) it is due to  $\beta$ -globulin in connection with lipoid (Recant et al.),
- 3) it is due to  $\beta$ -globulin alone (Cohen and Thompson), and
- 4) it is due to lipoids and  $\beta$ - and  $\gamma$ -globulins (Kunkel and Hoagland).

Our studies, therefore, lend support particularly to the theory advanced by Kunkel and Hoagland, as we found thymol precipitation with  $\gamma$ - as well as with  $\beta$ -globulins (though much stronger with  $\beta$ - than with  $\gamma$ -globulin).

Unlike Kunkel and Hoagland, we have not been able to demonstrate that albumin, whether it came from controls or from patients with hepatitis, influences the precipitation of  $\gamma$ -globulin or of  $\beta$ - and  $\gamma$ -globulins, whereas serum contains substances which can increase the precipitation considerably. As Recant et al. as well as Kunkel and Hoagland have demonstrated the importance of lipoids for the reactions, we believe that it is probably the serum lipoids which have exerted an increasing effect on the precipitation.

### Summary.

Mercuric chloride and thymol precipitations were carried out on solutions of protein fractions in saline. These protein fractions have been isolated from the blood from patients with hepatitis and from controls according to Cohn's method.

Mercuric chloride was found to precipitate  $\gamma$ -globulin — and only this fraction — and the precipitation was found to be inhibited by albumin — more by albumin from controls than from patients with hepatitis.

Thymol precipitates  $\gamma$ -globulin and, to an even higher degree,  $\beta$ -globulin. Albumin does not influence the reaction, no matter whether the albumin is derived from patients with hepatitis or from controls.

The thymol titre is found to be directly proportional to the globulin concentration.

The reaction is increased by substances in the serum which do not belong to the protein fractions examined in the present investigation, but judging from the findings reported by other investigators, it seems reasonable to assume that these substances are lipoids.

### References.

1. Balint, P., and Balint, M.: *Biochem.*, 1942—43: 313: 210. — 2. Bjorneboe, M.: *Acta med. Scand.*, 1946: 124: 466. — 3. Christoffersen, N. R., and Rågård, H.: *Nord. Med.*, 1947: 34: 1388. — 4. Cohen, P. C., and Thompson, F.: *J. Lab. clin. Med.*, 1947: 32: 314. — 5. Cohn, Anson and Edsall: *«Advances in Protein Chemistry»*, 1947: vol. 3: 447. — 6. Gros, W.: *Ges. exp. Med.*, 1937: 101: 519. — 7. Kabat, E. A., Hanger, F. M., Moore,

- D. H. and Landow. H.: J. clin. Invest., 1943: 22: 563. — 8. Kunkel and Hoagland: Ibidem, 1947: 26: 1060. — 9. MacLagan, N. F.: Brit. J. Exp. Path., 1944: 25: 234. — 10. Moore, D. B., Pierson, P. S., Hanger, F. M., and Moore, D. H.: J. clin. Invest., 1945: 24: 292. — 11. Recant, L. E., Chergaff and Hanger, F. M.: Proc. Soc. Exp. Biol., N. Y., 1945: 60: 245. — 12. Staub and Jezler, A.: Klin. Wschr., 1935: 1638. — 13. Stolte, J. B.: Ned. Tijdschr. Geneesk., 1940: 84: 4887. — 14. Ucko, H.: Klin. Wschr., 1936: 1074. — 15. De Vries, A., Acta med. Scand., 1938: 98: 95. — 16. Wuhrmann, F., and Wunderly, C.: »Die Bluteiweisskörper des Menschen», B. Schwabe and Co., Basel: 1947, p. 170.
-

## Mercuric Chloride and Thymol Precipitation in Plasma and Serum.

By

K. ALBERTSEN and F. HEINTZELMANN.

(Submitted for publication May 20, 1949.)

The precipitate produced in the serum by the addition of mercuric chloride in the Takata-Ara reaction, in the mercuric chloride titration or in the thymol test consists of proteins. The degree of the mercuric chloride precipitation depends partly on the gamma-globulin concentration and partly on the proportion between albumin and globulin but the thymol reaction chiefly indicates the beta-globulin concentration (Albertsen, Christoffersen and Heintzelmann). The two reactions were performed on the sera from 197 patients, most of them suffering from hepatitis, and are compared in Table I. It shows that there is no regular relation between the two reactions other than the fact that an increased thymol titre (over 4 Maclagen units) is often associated with an abnormal mercuric chloride titre (under 1.50).

In Table II the mercuric chloride titres in the plasma (with heparin 0.1 %) and serum from 57 patients are compared. It shows that the mercuric chloride titre is always lower in the plasma than in the serum. When the mercuric chloride titre in the serum is markedly abnormal (about 0.70), the difference between the mercuric chloride titres in the plasma and in the serum is only slight, but the difference in cases with normal or slightly decreased mercuric chloride titre is variable and there is no regular relation between the values obtained for serum and for plasma.

In chronic hepatitis and cirrhosis of the liver — in which the mercuric chloride titre of the serum is always found to be considerably decreased — the difference between the plasma and serum values is only slight. This also applies to 2 cases of leukemia and 3 cases of acute hepatitis in the first stage. In the latter the difference between the plasma and serum value is usually marked, but in about 30 % it is relatively small (under 0.30) at least in the early stage of the disease. In nearly all cases the difference increases to over 0.50 with clinical improvement.

Table I.

*Comparison between Mercuric Chloride Titres and Thymol Titres in the Sera from 197 Patients.*

Mercuric-chloride titres	Thymol titration (Maclagan units)						
	0—8	8—16	16—24	24—32	32—40	40—48	48—56
0.50—0.75...	5	10					
0.75—1.00...	12	19	10	2	1	2	1
1.00—1.25...	68	48	13	3	2		
1.25—1.50...	134	81	24	2			
1.50—1.75...	147	34	4				
1.75—2.00...	65	5					
over 2.00 ...	17						

Table II.

*Comparison between Mercuric Chloride Titre in 0.1 % Heparin Plasma and in Serum from 57 Patients.*

The figures in bold type show the results in patients suffering from chronic hepatitis.

In plasma	Mercuric-chloride titre							
	in serum							
	2.00— 2.25	1.75— 2.00	1.50— 1.75	1.25— 1.50	1.00— 1.25	0.75— 1.00	0.50— 0.75	0.25— 0.50
0.25—0.50...			1	1	5	1		
0.50—0.75...		6	14	11	26 <sup>a</sup>	26 <sup>11</sup>	3 <sup>a</sup>	
0.75—1.00...	4	13	50	33	18 <sup>1</sup>	4 <sup>a</sup>		
1.00—1.25...	17	38	35	4				
1.25—1.50...	18	17	4		1			
1.50—1.75...	4							
1.75—2.00...								
2.00—2.25...								

In cholecystitis and cholelithiasis and in occlusion of the bile passages, in cardiac disease, acute infectious diseases and various forms of malignant disease the plasma and serum values nearly always show a considerable difference (over 0.50) and this is true even when the mercuric chloride titre in the serum is lowered considerably (to about 1.0). The same applies to a number of lesions — above all, peptic ulcer — in which the mercuric chloride titre in the serum is not decreased.

The same difference between the plasma and serum values is found when 0.01 % heparin is used.

The thymol titration behaves quite differently (Table III). Unlike in the findings for the mercuric chloride titre, the precipitate is smaller in the plasma than in the serum. The variation of the values obtained is less pronounced, and when these values are correlated with the clinical features we find that in all 5 cases of fatal chronic hepatitis confirmed by autopsy, the serum values are almost the same as the values obtained for plasma — and in some of them the plasma values are even higher than the serum values.

Table III.

*Comparison between Thymol Titration in 0.1 % Heparin Plasma and in Serum from 57 Patients.*

The figures in bold type show the results in patients suffering from chronic hepatitis.

in plasma	Thymol titration (Maclagan units)									
	in serum									
	0—4	4—8	8—12	12—16	16—20	20—24	24—28	28—32	32—36	36—40
32—36.....						1				1
28—32.....					1			1		
24—28.....					2		1	1		
20—24.....					1					
16—20.....					3		1			
12—16.....			1	1	2	3	1			
8—12.....			2	1	6		1			
4—8.....		1	12	12	6					
0—4.....	95	61	42	14	1					

In patients suffering from acute hepatitis, however, the thymol values are usually much lower in the plasma than in the serum. Only in 5 patients, in 2 of whom the disease took a more subacute course, were high thymol values found in the early stage of the disease both in plasma and serum, but in these patients — as well as in the other patients with acute hepatitis who showed an increased thymol titre — the thymol values in the plasma subsided rapidly during the convalescence, so that the coefficient of thymol serum value: thymol plasma value increases with the clinical improvement of the patient.

When 0.01 % heparin was used the thymol values were about the same in plasma and in serum in most cases.

### Conclusion.

The mercuric chloride and thymol-precipitating reactions are essentially different. The mercuric chloride precipitation values are higher in the plasma than in the serum, but the thymol precipitation values are lower in plasma than in serum.

The results from both reactions in the serum and in plasma to which heparin is added may be used for diagnosis and prognosis, as in chronic hepatitis or cirrhosis of the liver the difference between the mercuric chloride titre in the serum and in the plasma is only slight, while it is considerable in obstructive jaundice. This also applies to generalized malignant disease. In acute hepatitis the difference increases with clinical improvement.

In fatal chronic hepatitis, when the thymol titre is increased, there is no difference between the serum value and the plasma value. This is in contrast to acute hepatitis and this observation may be used in the assessment of prognosis.

For references see the preceding paper by Albertsen, Christoffersen and Heintzelmann, in this journal.

From the Medical Department B, Frederiksberg Hospital, Copenhagen  
(N. R. Christoffersen, M. D.).

## The Influence of Heparin on the Precipitation of Serum Proteins by Mercuric Chloride and Thymol.

By

K. ALBERTSEN and F. HEINTZELMANN.

(Submitted for publication May 20, 1949.)

It has long been known that heparin, like many other substances can alter the stability of protein solutions (FISCHER (3), Henriques and Klausen (4), Hooker and Boyd (5)), but the cause of this faculty has been a subject of heated discussion. In the present study we attempt to explain the difference which we found in the mercuric chloride and the thymol precipitations in the serum and in plasma to which 0.1 % heparin had been added (Albertsen and Heintzelmann (2)).

This difference may be due to the different composition of plasma and serum or to the anticoagulant chosen heparin.

We have therefore performed experiments on the serum from patients with a positive thymol reaction to which we added fibrinogen, thrombin and heparin in various concentrations. Fibrinogen and thrombin were prepared in the State Serum Institute from the blood of normal subjects (see the preceding paper by Albertsen, Christoffersen and Heintzelmann (1)).

The technique employed in our mercuric chloride and thymol titrations is fully stated there. Fibrinogen and thrombin, in dry powder form, were dissolved in the serum; for the experiments with heparin we used Sol. heparini fortior (Leo) 5 %.

We first examined the influence of *fibrinogen* upon the reactions. Solutions of fibrinogen in saline in concentrations of 0.01—0.05—0.1—1 and 2 % gave negative thymol reactions, and it required a concentration of 1 % to produce precipitation with mercuric chloride (titre 1.0). The results from mercuric chloride and thymol titrations in the sera in which fibrinogen was dissolved in various concentrations after the addition of 0.15 % heparin in order to prevent coagulation are recorded in Table I.

Table I.

*Mercuric chloride and thymol titration of various sera in which fibrinogen is dissolved in concentrations of 0—0.05—0.5—1.0 and 2 %. 0.1 % heparin are added to the serum. For comparison, corresponding titrations are performed on 0.1 % heparin plasma from the same patients.*

Fibrinogen %	Mercuric chloride titration in ml. of 0.1 % mercuric chloride						Thymol titration (MacLagan units)					
	Serum and heparin 0.1 %					Plasma and heparin 0.1 %	Serum and heparin 0.1 %					Plasma and heparin 0.1 %
	0	0.05	0.5	1.0	2.0		0	0.05	0.5	1.0	2.0	
No. 1	1.00	1.00	1.00	0.95		0.75	19.8	18.1	17.8	18.5		10.4
— 2	0.75	0.80	0.85	0.75	0.75	0.70	15.3	16.1	14.0	14.0	5.5	11.5
— 3	0.70	0.70	0.75	0.75		0.75	11.9	12.0	12.0	10.8		9.3
— 4	1.05	1.05	0.90	0.95	0.85	0.85	30.6	33.9	28.5	26.6	22.7	25.9
— 5	1.35	1.45	1.40	1.35		1.15	12.3	11.9	10.8	5.5		4.5
— 6	1.45	1.45	1.35	1.30	1.25	1.20	16.8	15.5	15.4	8.3	5.3	6.0
— 7	1.60	1.55	1.20	1.30	1.25	1.10	8.6	8.0	6.9	4.9	6.4	2.5
— 8	1.15	1.15	1.15		1.15	0.95	10.6	11.7	10.3		6.6	6.8
— 9	1.05	1.05	0.95	0.95	0.95		6.8	5.5	3.5	2.6	1.0	
— 10	1.50	1.45	1.45	1.35	1.35		7.3	3.7	5.0	2.1	0.0	

Table I also shows that the addition of fibrinogen produces changes in the precipitating reactions similar to those when plasma to which heparin was added, was used instead of serum: an increase in the mercuric chloride precipitation (lower titres) and a decrease in the thymol precipitation (also lower titres). These changes usually appear only at a fibrinogen concentration of at least 1—2 %, *i. e.* in higher fibrinogen concentrations than are normally encountered in the plasma. When comparing these titres given by plasma to which 0.1 % heparin had been added, a change is observed which corresponds to the titres obtained by the addition of at least 1—2 % fibrinogen.

Correlation of mercuric chloride and thymol titres in sera and in citrated and oxalated plasma from the same patients showed lower titres in plasma than in sera — *i. e.*, increases in mercuric chloride precipitation and decreased thymol precipitation, but the changes were not so marked as in the heparin-plasma solution.

Experiments with thrombin dissolved in serum in the same way as mentioned for fibrinogen showed no changes in the titre.

These experiments show that the changes in the mercuric chloride and thymol reactions cannot be attributed only to differences in the composition of plasma and serum.

Our experiments also showed that the mere addition of heparin to the serum brought about some changes and therefore we investigated the *influence of heparin* upon the reactions. At first we carried out experiments in which the plasma was obtained without the addition of anticoagulants, *e. g.* by centrifugation of the sample of blood immediately after withdrawal. This examination was possible, however, only for the thymol test because the plasma coagulated during the titra-



Table II.

*Mercuric chloride and thymol titration of plasma obtained without anticoagulant, with heparin added in concentrations 0—0.01—0.1 and 0.5 %. For comparison, corresponding titrations are performed on serum from the same patient with the addition of the same heparin concentrations.*

	Mercuric chloride in ml				Thymol (Maclagan units)			
Heparin % .....	0	0.01	0.1	0.5	0	0.01	0.1	0.5
Plasma .....	—	0.80	0.70	0.70	17.2	11.8	6.9	3.0
Serum .....	1.20	1.20	0.90	0.90	17.2	20.6	14.1	4.9

tion with mercuric chloride. At the same time heparin in varying concentrations was added to portions of the plasma.

Table II shows the results obtained in one experiment and others gave the same result. For comparison we have also recorded the results of the titration on the serum to which heparin in varying concentrations had been added.

Table II also shows that the thymol values obtained for serum and plasma without heparin are very similar and this indicates that fibrinogen in the blood does not influence the thymol precipitation. As mentioned above a similar comparison by mercuric chloride precipitation has not been possible.

The addition of heparin brings about a distinct change in the reactions. In the plasma the thymol titre decreases gradually with increasing concentration of heparin. In the serum, in addition, there is a slight increase in the titre at a heparin concentration of 0.01 %, but at the higher heparin concentration lower values are recorded, though the titre in the serum does not reach the low levels as in the plasma. This difference between plasma and serum might suggest that fibrinogen influences the thymol precipitation by combination with heparin. In the mercuric chloride precipitation, even a heparin concentration of 0.01 % shows a very marked decrease in the plasma titre, which might indicate that this change is largely due to the presence of fibrinogen. The addition of heparin produces a decrease in the mercuric chloride titre in the serum.

Table III records the results of experiments with the addition of heparin in various concentrations to sera from patients with positive mercuric chloride and thymol reactions. It shows that heparin causes a slight increase in the mercuric chloride precipitation, i. e., a lower titre, though not as low as the values obtained with a heparin concentration of 0.1 %. They correspond throughout to the values obtained by titration of a 0.1 % heparin-plasma solution from the same patients.

The thymol reaction is influenced in the opposite direction, as heparin causes a decrease in the precipitation. A concentration of 0.01 % of heparin produces no definite change and the titres varied only slightly. An addition of 0.05 % heparin produces in most sera a distinct decrease in titre, and the addition of 0.1 % produces in most cases a similar titre as that obtained in a 0.1 % heparin-

Table III.

*Mercuric chloride and thymol titration of various sera with the addition of heparin in concentrations of 0—0.01—0.05—0.1 and 0.5 %. For comparison, corresponding titrations are performed on 0.1 % heparin plasma from the same patients.*

Heparin %	Mercuric chloride titration in ml. of 0.1 % mercuric chloride						Thymol titration (MacLagan units)					
	Serum					Plasma with 0.1 % heparin	Serum					Plasma with 0.1 % heparin
	0	0.01	0.05	0.1	0.5		0	0.01	0.05	0.1	0.5	
No. 1	0.90	0.85	0.70	0.70	0.65	0.70	23.0	20.4	26.2	26.8	13.6	23.4
— 2	0.90				0.75	0.75	17.5	18.8	24.5	23.6	11.6	17.7
— 3							12.2	13.9		16.8	5.7	11.5
— 4	0.75	0.75	0.75	0.75	0.65	0.65	15.5	13.6	12.9	10.9	6.6	11.9
— 5	0.75				0.70	0.70	15.7	16.1	13.3	12.4	6.7	12.4
— 6	0.95	0.90	0.95	0.85	0.75	0.85	29.3	28.3	27.4	26.0	10.5	24.2
— 7	0.95				0.75	0.80	24.4	23.5	24.1	22.3	11.4	15.4
— 8	1.10	1.05	0.90	0.85	0.70		34.3	30.6	34.0	31.1	18.0	
— 9	1.45				1.05	1.10	23.7	22.6	22.7	19.3	7.5	15.4
— 10	0.95	0.95	0.90	0.90	0.85	0.80	19.9	21.2	15.5	13.1	3.7	14.2
— 11		1.35	1.20	1.20				12.0	17.8	4.7		
— 12	1.45	1.45	1.25	1.25		1.25	14.0	16.8	14.2	8.7		13.0
— 13	1.40	1.30	1.25	1.20	1.25	1.20	7.2	6.8		3.0	1.3	3.0
— 14	1.55	1.55	1.50	1.45	1.40	0.95	11.5	11.8	8.8	9.1	2.0	3.1
— 15	1.90				1.45	1.40	10.8	11.9	9.2	6.4	2.4	5.0
— 16	1.90	1.60	1.35	1.35	1.30	1.05	8.0	8.7	6.7	5.4	2.2	6.9
— 17	1.95	1.40	1.30	1.25	1.30	1.15	7.8	8.1	6.6	4.5	1.9	2.2
— 18	1.20	1.20		0.90	0.90		15.5	20.6		14.1	4.9	
— 19	1.55	1.50		1.05	1.05		15.6	14.7		10.6	5.0	
— 20	1.15	1.10	1.05	0.95		0.95	15.4	10.4	8.3	6.9		7.0

plasma solution from the same patient. The addition of 0.5 % heparin causes a very definite fall in the titre, but in 1 patient (who died of chronic hepatitis) an increased titre at a heparin concentration of up to 0.1 % occurred in all 3 tests on serum obtained at intervals of a week (Nos. 1—3).

Finally we examined the effect of heparin on the mercuric chloride and thymol precipitations in solutions of the individual globulin fractions (cf. Albertsen, Christoffersen and Heintzelmann (1)). The addition of heparin to solutions of  $\gamma$ - and  $\beta$ - +  $\gamma$ -globulins in saline produced an increased precipitation with mercuric chloride (lower titres), and the same reactions were given by solutions of  $\gamma$ - and  $\beta$ - +  $\gamma$ -globulins with albumin.

The influence on the thymol precipitation of the addition of heparin varies with the individual globulin fractions, as shown in Table IV. In solutions of  $\beta$ -globulin in saline the addition of heparin caused a decrease in the thymol precipitation and the titres decreased with increasing heparin concentration. The solutions, however, were not clear, and even though correction was made for turbidity — by determination of the extinction values for the solutions without thymol and subtracting this value from the extinction values after the addition of thymol — the results must be accepted with reservation. The inhibitory influence of heparin, however, is unquestionable. In solutions of  $\gamma$ -globulin the addition of heparin causes a distinct increase in the precipitation which increases

Table IV.

*Thymol titration of  $\beta$ ,  $\gamma$  and  $\beta + \gamma$ -globulin solutions in saline with addition of heparin in concentrations 0—0.01—0.1 and 0.5 %.*

Heparin %	Thymol titres (Maelagan units)			
	0	0.01	0.1	0.5
$\beta$ -globulin 3 % .....	12.8	12.2	10.3	7.2
" 5 % .....	19.0	19.5	15.5	14.4
$\gamma$ -globulin 5 % .....	3.3	5.5	15.2	8.6
$\beta$ and $\gamma$ -globulin 5 % .....	10.0	10.3	12.2	8.1
" " " 10 % .....	23.0	25.9	31.5	23.2

with the heparin concentration, up to 0.1 %. Further addition of heparin (0.5 %) produces a lower titre still even though the titres do not fall as low as those produced by the  $\gamma$ -globulin solution without heparin.

In  $\beta$ - +  $\gamma$ -globulin solutions (containing about equal parts of  $\beta$ - and  $\gamma$ -globulin) the addition of heparin in a concentration of up to 0.5 % causes no particular changes in the titre in solutions with 5 % globulin, while it causes an increasing precipitation in solutions with 10 % globulin up to a heparin concentration of 0.1 %. In higher concentrations there is again a fall in the titre, so that the addition of 0.5 % heparin produces the same thymol titre as solutions free of heparin.

In solutions of globulin with albumin the addition of heparin brought about the same changes in the thymol precipitation.

These experiments lead us to conclude that heparin increases the protein precipitation in sera, plasma and in solutions of proteins in saline brought about by mercuric chloride. Conversely the addition of heparin lowers the thymol precipitation of protein in serum and plasma — just as it lowers the thymol precipitation in saline solutions of  $\beta$ -globulin. In contrast, the addition of heparin in low concentration causes an increase in the thymol precipitation in saline solutions of  $\gamma$ -globulin.

That the mercuric chloride titre in a heparin-plasma solution (as shown in the preceding paper (2)) is lower than in the serum, is not due to heparin alone, as the same effect may be attributed to fibrinogen. The decreased thymol precipitation observed in heparin-plasma solutions in the serum of patients, with the exception of cases of chronic hepatitis is also due to the inhibitory effect of heparin upon the thymol reaction.

It is possible that fibrinogen may exert an influence here also. The results recorded in Table II might indicate that fibrinogen exerts its effect through a combination with heparin.

In patients with chronic hepatitis we found the thymol titres in the plasma almost unchanged or only slightly increased as compared with the titres obtained in sera. This would contradict the findings on the effect of heparin on the thymol reaction. In patients with chronic hepatitis the mercuric chloride titre is always decreased considerably (*i. e.*, the precipitation is increased). It has been shown (Albertsen, Christoffersen and Heintzelmann (1)) that this precipitation depends

partly on the  $\gamma$ -globulin concentration and partly on the ratio between the albumin and the  $\gamma$ -globulin content of the solution examined, and it has been shown that  $\beta$ - as well as  $\gamma$ -globulin is precipitated by thymol and this fact, together with the finding that heparin in lower concentrations (up to 0.1 %) increases the thymol precipitation of  $\gamma$ -globulin, while the precipitation of  $\beta$ -globulin is reduced, could explain the problem in the following way: In patients with chronic hepatitis the increased thymol titre (and lowered mercuric chloride titre) is due to an increase in the  $\gamma$ -globulin content. In patients with acute hepatitis the thymol titre is increased, but the mercuric chloride titre is usually normal or only slightly reduced and therefore the thymol titre would be due to an increase in the  $\beta$ -globulin content. This thesis agrees with the conclusions drawn by Kunkel and Hoagland (6) about the part played by the  $\beta$ - and  $\gamma$ -globulins in the thymol reaction. These authors stated that the thymol reaction in the early stages of hepatitis depends on the lipoid and lipo-globulin ( $\beta$ ) content of the serum and during the later stages on the globulin content.

#### References.

1. Albertsen, K., Christoffersen, N. R. and Heintzelmann, F.: *Acta med. Scand.* **136**: 362, 1950. - - 2. Albertsen, K. and Heintzelmann, F.: *Acta med. Scand.* **136**: 313, 1950. - - 3. Fischer, A.: *Biochem. Z.*, **244**, 464, 1932. - - 4. Henriques, F. and Klausen, U.: *Biochem. Z.*, **254**, 414, 1932. - - 5. Hooker, S. B. and Boyd, W. C.: *J. Biol. Chem.*, **100**, 187, 1933. - - 6. Kunkel, H. G. and Hoagland, C. H.: *J. clin. Invest.*, **26**, 1060, 1947.



From the Medical Department of the Hälsingborg Hospital, Sweden.  
(Director: Prof. Thor Stenström.)

## Paroxysmal Tachycardia which the Patient was Momentarily Able to Produce Himself.

By

OLOF FORSSMAN and HANS STENQVIST.

(Submitted for publication April 6, 1949.)

---

Paroxysmal tachycardia is not as a rule caused by intervention of the will. Only very few cases have been described where the subject was able to accelerate the action of the heart at a given command by concentrated will power without visible muscular efforts or emotional influences from without.

The first such case was described by Tuke (1872). Both in this and subsequent cases reported in the literature by Tarchanoff (1885), Pease (1889) and van der Velde (1897) the increase in the frequency of the heart beat due to will power was only moderate. Koehler (1914) produced tachycardia in himself and this was associated with an increase of the blood pressure and the respiration rate. He considered that it was due to increased tone of the sympathetic and decreased tone of the vagus. Favill and White (1917), West and Savage (1917), and Taylor and Cameron (1922) came to the same conclusion in their various cases, in which the acceleration of the heart beat was combined with mydriasis and a rise in blood pressure. After the injection of atropine (2 mg—1/30 grain) the heart rate increased even during rest but a reduced faculty to increase it still further voluntarily persisted. In Favill and White's case an electrocardiogram showed, that during the attacks of tachycardia, the R, S and T-waves altered. Carter and Wedd (1918) mentioned a patient who was unable to produce any voluntary increase in the action of the heart under the influence of atropine. The electrocardiogram indicated an ectopic rhythm with a focus in the upper part of the right atrium under the control of subjective inhibiting reflexes but not influenced by vagal stimulation. Carpenter, Hoskins and Hitchcock (1934) described a person who could increase his basal metabolism without visible muscular efforts. There was also a rise in blood pressure and a moderate increase in the pulse rate. Electrocardiograms

were not taken. In the cases described by Ogden and Schock (1939) the voluntarily induced tachycardia was accompanied by increases in the blood pressure, respiration rate, respiratory volume, intake of oxygen and output of carbon dioxide. Feil, Green and Eiber (1947) described a patient with Wolff-Parkinson-White-syndrome, in whom adrenalin (0.5 ml of a 0.1 % solution), or atropine (2 mg) or ergotamine tartrate given subcutaneously did not inhibit the faculty to increase the heart rate voluntarily. The authors believed that the cause of this probably is a stimulation of the sympathetic, but that a lower tone of the parasympathetic also played a certain part.

We have observed a patient who was able to produce paroxysmal tachycardia in himself. This case differs from the cases in the literature because the patient was not able to induce the attacks by concentration of the will. Less directly, however, his will did participate in the mechanism causing the attacks, as through certain simple voluntary actions, such as deep inspirations, pushing forward of the abdominal musculature while holding his breath, swallowing and occasionally also through a Valsalva's manoeuvre he was able momentarily to produce a very pronounced tachycardia.

A 36-year-old mechanic did not as far as is known suffer from paroxysmal tachycardia. There were no cardio-vascular diseases in the family. He had previously been healthy. Lately he had been restless and mentally depressed, partly owing to the pressure of work in shift. He smoked about 20 cigarettes per day and had not changed his brand of cigarettes recently. Before the present symptoms appeared he had no palpitations, was not short of breath and his ankles were not swollen. There was no nycturia or angina pectoris. In December 1946 the patient suddenly began to be troubled by attacks of tachycardia which he himself was able to produce in one of the following ways:

By deep inspirations.

By pushing forward his abdominal musculature, without straining and while holding his breath.

By swallowing coarser, badly chewed food.

The patient himself thought that it felt as if the attacks lasted only as long as the food was in the oesophagus.

Physical exertion, on the other hand, did not give rise to any attacks. Occasionally he suffered from involuntary tachycardia without demonstrable cause.

He was treated in the Medical Department of the Hålsingborg Hospital during two periods and the following examinations were carried out: When admitted on 7. 1. 1947 his general condition was good and there was no evidence of loss of weight. At rest he was not cyanosed or dyspnoic, and there was no oedema. No fremitus. The heart measured 13 cm across. There was a short systolic basal murmur and the second pulmonary sound was accentuated. Under ordinary conditions the heart rhythm and frequency were normal. When the patient held his breath and pushed forward his abdominal musculature tachycardia resulted immediately, though the rhythm remained regular. The heart rate was about 200, as against 70 at rest. When the patient relaxed his abdominal musculature the heart rate returned to normal immediately. The patient could also produce tachycardia by breathing in or by swallowing some water, but under these conditions it lasted only a few seconds. The other organs were normal.

Other investigations: Hemoglobin 110 %, RBC. 4.14 million, WBC 4,800; Neutrophils 40 % (including 3 % stab cells), eosinophils 5 %, basophils 1 %, monocytes 11 %, lymphocytes 43 %. Sedimentation rate 3 mm/hr.

Non-protein-nitrogen 37 mg %. Urine: normal. Wasserman and Kahn tests negative. Fractional test meal: normal amount of acid.

Barium meal: normal stomach. No signs of diaphragmatic hernia.

The pulse rate was observed on several occasions, with the following results: Pulse rate (patient in the prone position at rest) 81/min.; on standing 100/min. After the patient had produced his tachycardia, the pulse rate was (in prone position) 160/min., and on standing 176/min.

Blood pressure (patient in the prone position at rest) 125/70—130/75 mm Hg. When the patient stood up the systolic blood pressure was about 5 mm higher than at rest. During the attacks of tachycardia no definite change in the blood pressure was found as compared with the figures for rest. Neither the pulse rate nor the blood pressure were affected by pressure on the carotid sinus.

Venous pressure, both at rest and during attacks of tachycardia was 7.5 cm.

Radiograph of chest reported by the radiologist Dr. O. Müller: »The transverse diameter of the heart, measured at a distance of 2 m, was 12 cm, of which 8 cm, was to the left of the midline. The transverse thoracic diameter was 31.5 cm. Nothing abnormal in the lung fields.» Subsequent radiographs showed no radiological difference in the size of the heart from the normal in the tachycardiac phase. Even when the mucous membrane of the pharynx was anaesthetized, the patient was able to produce tachycardia. During oesophagoscopy (carried out by Dr. W. Behrman) the patient had tachycardia as long as the instrument was in the oesophagus.

Gynergen and prostigmine tests: after  $\frac{1}{2}$  mg of gynergen intravenously the resting pulse rate fell from 85 to 60/min., but the patient's ability to produce tachycardia was not inhibited. A slight rise in the blood pressure after gynergen (110/65—130/85—115/80).

After injecting 1 mg prostigmine subcutaneously the resting pulse rate fell from 82 to 70/min., but the blood pressure did not alter. The patient was still able to produce tachycardia as before.

Dr. K. Liedholm (Docent at the Lund Medical Clinic) and Dr. H. Bjerlöv (of Stockholm) have helped us to interpret the patient's electrocardiogram, for which we are grateful. The electrocardiograms taken at rest have been found normal in all respects. There was no evidence of the Wolff-Parkinson-White-syndrome. During the tachycardia the electrocardiograms showed changes which varied on different occasions. These appeared particularly in the QRS-complex. During the time before the tachycardia the P-waves were normal, though some of them were a little atypical. At the peak of the tachycardia on the other hand, P-waves could not be distinguished and the rapidity of the heart rate made reading difficult. Several electrocardiograms give the impression of rather regular flutter waves overrunning the QRS-complexes. Irregular high-frequency waves of varying sizes indicated fibrillation. The QRS-complexes in electrocardiograms taken during tachycardia, did not always show an identical appearance. Somewhere one finds periods of alternating type.

The patient was discharged home after a stay of 17 days. Treatment consisted of bellergal and instructions concerning stay in bed. After discharge, however, his condition became worse, as he noticed that the attacks of tachycardia also came on straining. After a fortnight at home he was therefore readmitted. The findings on his admission were essentially the same as those noted previously with the difference, that the patient could now bring on tachycardia by carrying out Valsalva's manoeuvre.

Increasing doses of quinidine were given and at an early stage of this treatment the patient noticed that it was more difficult to produce tachycardia, and that the heart rate was then not as high as previously. After a short time on a daily dose of 2 g of quinidine, the patient lost his ability to produce tachycardia and it was possible to decrease the dose gradually, and after a stay of 40 days treatment was discontinued and the patient went home improved.

Electrocardiograms taken before his discharge, as well as later on (the last about a year after his second stay in hospital) have been normal, even under conditions which earlier on had produced tachycardia. With the exception of a short period after his discharge, the patient has been able to do his work.



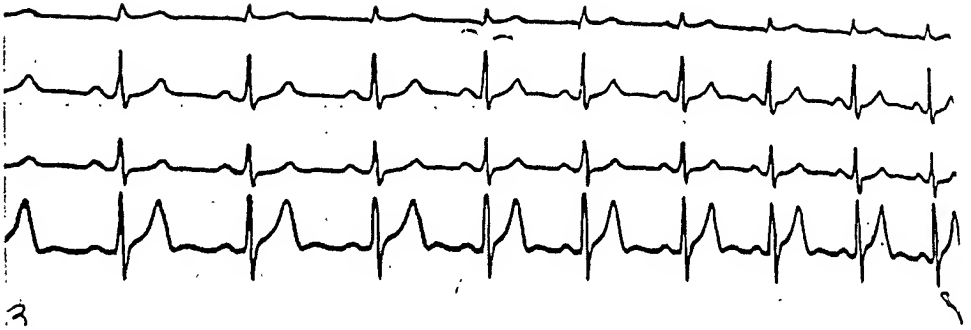


Fig. 1. Ekg taken in rest (prone position).

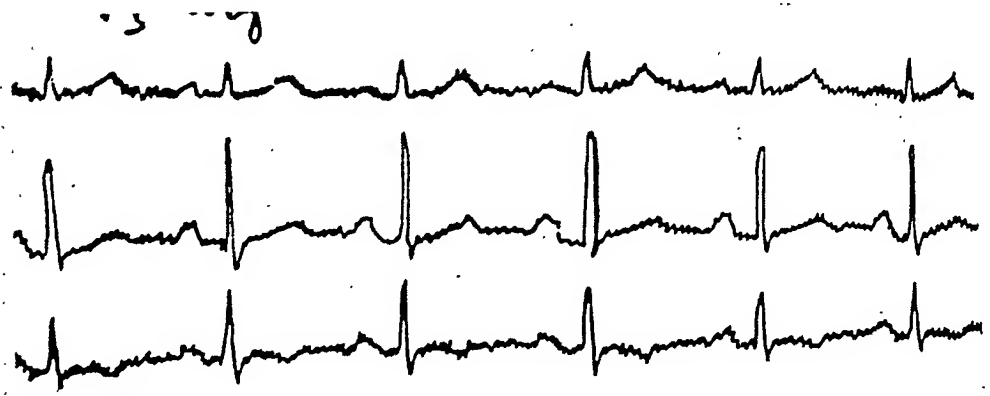


Fig. 2. Ekg taken in rest (standing).

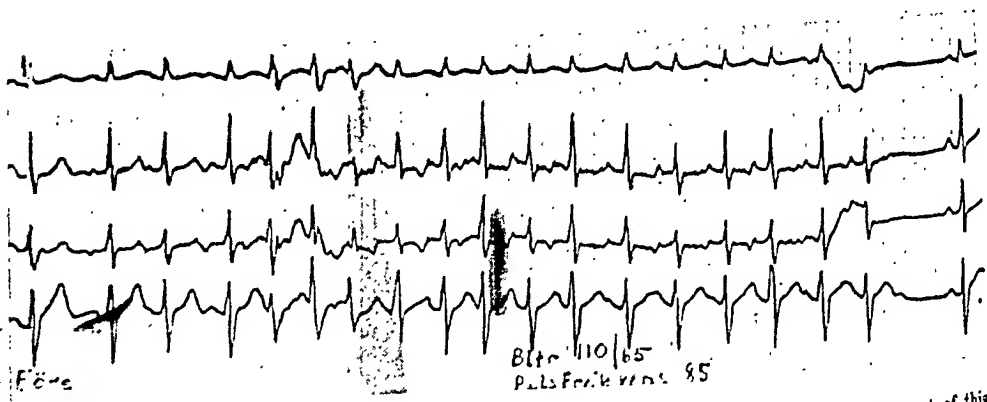


Fig. 3. Ekg taken after that the patient had released his tachycardia. The first part of this and following ekg is taken with the patient in rest, the middle part after his having released his tachycardia and the final part when returning to the state of rest.

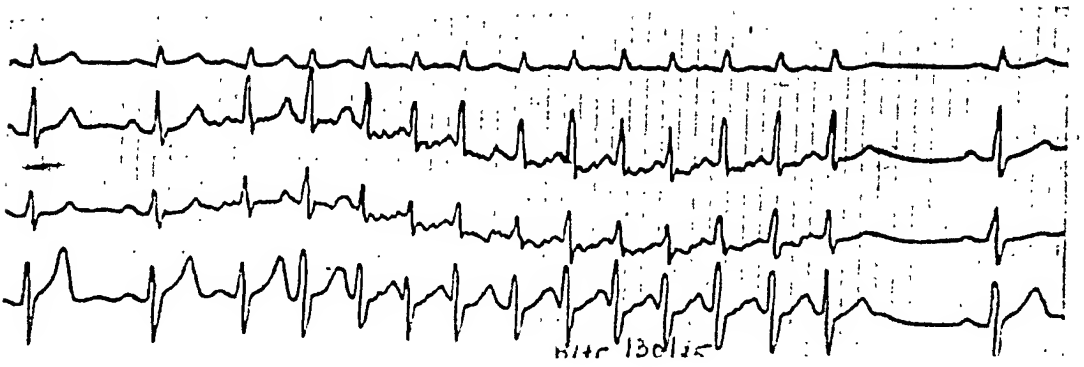


Fig. 4. Ekg taken 30 minutes after administration of gynergen.

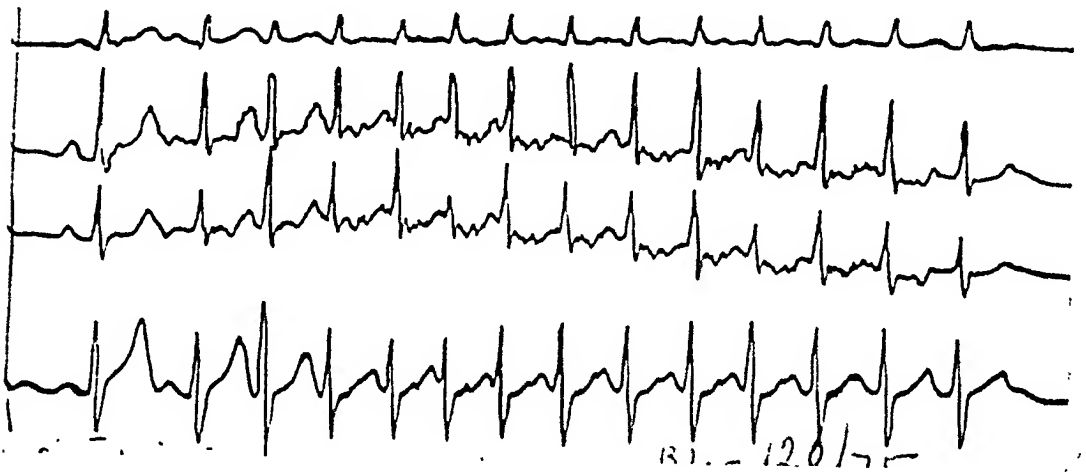


Fig. 5. Ekg taken 20 minutes after administration of prostigmine.

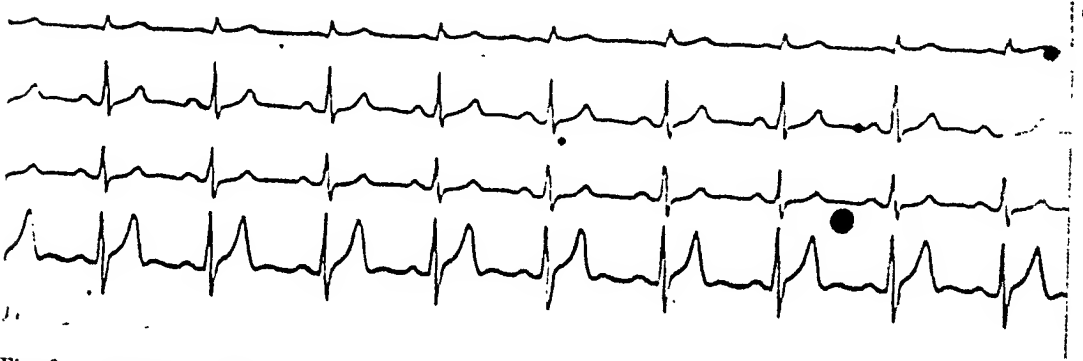


Fig. 6. Ekg taken while the patient is trying to produce tachycardia after the quinidine therapy having been discontinued.

The case reported here was a healthy man who developed heart trouble in the form of palpitations brought on by swallowing, by pushing forward of the abdominal musculature and at the same time holding his breath, by deep inspirations or during a later phase of the illness, by performing Valsalva's manoeuvre. The tachycardia which was recorded by electrocardiograms was not affected by pressure on the carotid sinus or by ergotamine tartrate or prostigmine. Anaesthesia of the mucous membrane of the pharynx did not prevent the onset of the tachycardial attacks. The symptoms were reduced and finally abolished by quinidine, and they have not recurred even since the cessation of quinidine treatment.

The patient was unable to produce his attacks of tachycardia directly by psychic concentration, and they cannot therefore be called voluntary in the strict sense of the term. An active act of will if only indirect was, however, necessary for their production. (The attacks produced by swallowing must be classed apart.) Bearing in mind the importance of the thoracic and abdominal regions in the production of ordinary forms of tachycardia it is easy to understand that in our attempts to find an explanation of the causal factors concerned we directed our attention to the pathological conditions occurring in these regions which can give rise to involuntary attacks of paroxysmal tachycardia. Several of these are known: diaphragmatic hernia, chronic peptic ulcer, various diseases of the bile ducts, appendicitis, mediastinal and pulmonary diseases and tumours of the carotid body. In conditions without demonstrable pathological lesion, such as distended stomach, attacks of tachycardia may arise. Examination of our patients showed, however, that there was no evidence for any of these conditions (radiographs of mediastinum, lungs, and stomach and acid values in the gastric juice were all normal).

It is hardly necessary to point out that in one way or another the attacks were caused by a reflex-mechanism. The patient's marked neurosis together with a considerable abuse of nicotine may have contributed to the possibility of an increased tone of the sympathetic. Tachycardia coming on after deep inspirations might analogous to respiratory arrhythmia, be explained by an increased predominance of sympathetic or by the increased filling of the large veins and the right atrium, which in turn causes tachycardia in order to overcome the extra venous supply (Bainbridge's reflex). In Valsalva's manoeuvre which in the later stage of the patient's illness caused a marked increase of the heart rate, there is an increased sympathetic tone followed by an increased vagal tone (Liedholm and others). It is, however, obvious that in the present case the marked effect of deep inspiration and of Valsalva's manoeuvre on the heart rate far exceeded normal limits.

In order to form an idea of the reactivity of the vegetative system in our patient, various attempts were made to upset the autonomous reflex-mechanism by pressure on the carotid sinus, and by injections of ergotamine and prostigmine, and by blocking the nerve-endings of the mucous membrane of the pharynx by cocaine anaesthesia. This did not, however, inhibit the patient's ability to produce the cardiac attacks. So as not to risk worsening of the patient's state atropine was not given for experimental purposes. In the cases reported by Favill and White, West and Savage and Taylor and Cameron it was found that despite the relatively large

dose of atropine (2 mg) it was impossible to produce complete paralysis of the branches of the parasympathetic nerve-endings.

In our patient, the investigations on the part played by the autonomous nervous system have not given any definite result, even if an increase of the tone of the sympathetic seemed likely. The question arose therefore whether changes in the heart itself might contribute to the production of the tachycardial attacks.

Jervell has advanced an interesting hypothesis concerning the causes of involuntary paroxysmal tachycardia, transient flutter and fibrillation. He states that it is probable that provoking and predisposing factors exist. The provoking factor is extra-cardiac; and according to Jervell caused by disorders in the vegetative nervous system, usually by an increased tone of the sympathetic such as occurs in pathological conditions mentioned above. The predisposing factor can be traced to structural changes in the specific musculature of the heart, including toxic damage, degenerative and inflammatory changes or functional conditions of an unknown nature. It is only by the simultaneous action of both factors that paroxysmal tachycardia, fibrillation or heart flutter arise. In case of more extensive structural changes in the heart muscle the provoking factor is probably only slight.

It is interesting that in the present case there actually occurred a distinct disturbance in the cardiac conduction during the attacks of tachycardia as was clearly shown by the electrocardiograms. Whether this was of an organic or functional nature was difficult to decide, as the electrocardiograms taken at rest were normal. These changes in the conductive system of the heart might therefore constitute Jervell's predisposing factor. The provoking factor appeared during the act of swallowing or through certain other acts carried out by the patient himself. To judge by all the evidence, the predisposing factor was eliminated by quinidine, and the patient then lost the ability to produce the tachycardial attacks.

### Summary.

After a review of cases of voluntary paroxysmal tachycardia reported in the literature, the authors give an account of a case of their own, in which attacks were not produced by an act of mental concentration, though the will of the patient did indirectly play a part, as he was able to produce a rapid heart-action by certain simple voluntary actions (deep inspirations, pushing forward of the abdominal musculature while at the same time holding his breath, swallowing and during a later phase of the illness by performing Valsalva's manoeuvre). The tachycardia was not affected by pressure on the carotid sinus nor by ergotamine tartrate or prostigmine. With daily doses of quinidine the symptoms disappeared, and they have not, during a follow-up period of more than a year, reappeared though quinidine was no longer given. The etiology of the attacks is discussed and the hypothesis is put forward that in this case it may have been a matter of combination of a disturbance of the conduction of the heart with an extra-cardiac factor, the latter probably being increased tone of the sympathetic.

## References.

Tuke: »Influence of the mind upon the body.» London, 1884, p. 162. — Tarchanoff: Arch. ges. Phys., 35: 109: 1885. — Pease: Boston Med. Surg. J., 120: 525: 1889. — Van der Velde: Arch. ges. Phys., 66: 232: 1897. — Koehler: Arch. ges. Phys., 158: 579: 1914. — Favill and White: Heart, 6: 175: 1917. — West and Savage: Arch. Int. Med., 22: 266: 1918. — Carter and Wedd: Arch. int. Med., 22: 571: 1918. — Taylor and Cameron: Amer. J. Phys., 61: 385: 1922. — Carpenter, Hoskins and Hitchcock: Amer. J. Phys., 110: 320: 1934. — Ogden and Schock: Amer. J. Med. Sci., 198: 329: 1939. — Liedholm: Acta Med. Scand., Suppl. CVI 1939. — Jervell: Acta Med. Scand., CXXV: 295: 1946. — Feil, Green and Eiber: Amer. Heart J., 34: 334: 1947.

---

From the Eighth Department of Medicine (Director: Dr. C. Müller) and  
the Pathological Department (Director: Dr. E. Hval).  
Ullevål Hospital, Oslo.

## **Acute Necrosis of the Renal Papillae in Pylonephritis; Particularly in Diabetics.**

By

VIKTOR GAUSTAD and JOHAN HERTZBERG.

(Submitted for publication June 29, 1949.)

Acute necrosis of the renal papillae in cases of pylonephritis is fairly rare and almost always fatal. It is often associated with diabetes and should be recognized as an important and serious complication in elderly diabetics. Edmondson et al. (1) recently made an extensive study of this condition which is only rarely reported in the Scandinavian medical literature. We wish to record 6 cases observed at Ullevål Hospital, Oslo.

Friedreich (2) (1877) first described acute necrosis of the renal papillae. His account of the macroscopic changes included all the stages also the complete discharge of the necrotic papilla. The patient observed by him had hypertrophy of the prostate and hydronephrosis, but no diabetes. Günther (3) first pointed out the part played by diabetes in the development of acute papillary necrosis. Of the 42 cases of this condition found in diabetics so far published, 29 were included in Edmondson's study. The present paper is the first to report it in the Scandinavian literature. As necrosis of the renal papillae varies with the presence or absence of diabetes, we wish to discuss this condition as it occurs in the former group, and then deal with the features distinguishing it from acute necrosis of the renal papillae in non-diabetics. Edmondson et al. examined 859 diabetics at autopsy. There were 107 patients who died of pylonephritis and in 29 (27.1 %) of these pylonephritis was associated with acute necrosis of the papillae. The renal lesion was bilateral in 18, unilateral in 8, and in 3 there was no definite record. There were 19 females and 10 males. The frequency of this condition increased with age, and only one patient was under 40. Obstruction of the urinary tract was rare. After attention had been drawn to this condition, it was detected more







more concentrated, and losing large quantities of water, chlorides and sugar. The high-molecular proteins remain and the osmotic pressure is therefore raised. The patient often suffers from some obliterating disease of the arterial tree which further reduces their blood supply. Diabetes also seems to play a part, particularly when accompanied by acidosis. Menkin (7) believed that an accumulation of acid in the tissues, common in diabetes, produces a change in inflammatory exudates. The polymorphonuclear cells are scanty and the mononuclear cells are relatively numerous.

The prognosis is grave and the condition usually fatal. There is no effective treatment for bilateral cases. In a case which recovered such as recorded by Edmondson et al. the disease is unilateral. They also described another such case in which nephrectomy was performed. Günther (1937) has reported 2 unilateral cases in which nephrectomy gave good results.

The condition is so serious that everything possible must be done to prevent infection of the urinary tract in diabetics. Catheterization should be carried out with the most careful aseptic precautions and only when really necessary. Infections of the urinary tract in diabetics must be treated with great care and with chemotherapy and anti-biotics. Sensitivity tests may be necessary. Other diseases of the urinary tract, such as renal calculi and hypertrophy of the prostate, should if possible be treated surgically as experience shows that obstruction of the urinary tract in diabetics is more dangerous than for other patients. The treatment of bilateral necrosis of the papillae is useless but in unilateral disease when diagnosed early enough, nephrectomy is indicated. It should not be disregarded by the prospect of necrosis of the papillae of the opposite side. The following 6 cases of acute necrosis of the papillae were recently observed at Ullevål Hospital:

*Case 1* (Ref. No. 2529/48): A woman of 80 suffered from diabetes since 1924, but did not require insulin. A renal calculus measuring  $2 \times 1.5$  cm was demonstrated on the left side in 1944. Urine was sterile and the blood pressure was 180/100 mm Hg. Because of her age operation was not considered. On admission on January 31st, 1948, for fracture of the thigh, diabetes was found to be severe. She was given 16 units of Retard insulin and was transferred to a medical ward where her sedimentation rate remained high (120 to 105 mm). Urographic examination on February 24th showed no change since 1944. The urine contained 0.1 % protein and gave a positive reaction for blood. At first there were only few leucocytes, but by March 5th they were numerous. The urine was sterile on February 17th but on March 19th Proteus was grown. On March 5th the blood urea was 55 mg %. Her temperature was slightly raised. The fundi were normal, but difficult to examine because of cataract. Between March 22nd and March 27th she was given 22.5 g sulphanilamide, but she became worse and her urinary tract symptoms were more marked. She was pale (a fall of hemoglobin from 82 % to 57 % occurred). Early in April, her temperature rose and she developed signs of uremia. The blood urea on April 9th was 201 mg %. A blood culture on the same day yielded Proteus. Her general condition became alarming and she developed extensive bed sores over the buttocks. The blood sugar rose, but there was no ketonuria. She died on April 12th.

Autopsy showed bilateral broncho-pneumonia, marked arteriosclerosis with calcification of the coronary arteries, and enlargement of the left kidney (290 g) with edema of the perirenal tissues. The capsule was thickened and adherent to them and it was also adherent to the kidney which had a finely granular surface. On section (Fig. 1) a stone measuring  $3 \times 2 \times 1$  cm was found in the renal pelvis which was considerably dilated.

and contained urine mixed with much pus. All the renal papillae were white, soft and necrotic. The tissues adjacent to the necrotic areas were bluish-black. The renal parenchyma contained many small abscesses, some of which were confluent. The right kidney was also enlarged (210 g). The capsule was adherent and thickened, and the renal pelvis was dilated and full of purulent urine. There were also small abscesses in the renal parenchyma. The mucous membrane of the bladder was inflamed and partially gangrenous. It contained stinking urine.

*Histological sections of the left kidney* showed necrotic, structureless renal papillae (Fig. 2). The necrotic tubules contained granular, blue clumps consisting of bacteria. The necrotic papillae were surrounded by a deep blue zone forming a fairly straight line of demarcation. This zone was densely packed with polymorphonuclear leucocytes, lymphocytes and plasma cells, which were partly degenerate (Fig. 3). The necrotic area did not extend along the columns of Bertin nor in a cortical direction, to the glomeruli. There were also severe changes in the renal parenchyma. The capsule was thickened and infiltrated with round cells. Some glomeruli showed hyaline degeneration, and others were shrunk; in a few there was some intercapillary glomerulo-sclerosis. There was considerable post-mortem degeneration of the tubules which were not dilated. The larger arteries showed arteriosclerosis with thickening of the intima. There was some thickening and hyaline degeneration of the walls of the afferent and efferent vessels. There was severe inflammation and marked abscess formation. Several clumps of bacteria staining blue were seen, and the leucocytes were chiefly polymorphonuclears, but in some places plasma cells were remarkably numerous, and lymphocytes and fibroblasts were also seen. Several small thrombi were attached to the walls of veins.

*Summary.* A woman of 80 suffered from diabetes. She was admitted to hospital for a fracture and pyuria developed which was due to *Proteus*. Uremia and hyperpyrexia occurred and *Proteus* was now grown from the blood.

Autopsy showed pyelonephritis most marked on the left side. There was a stone in the pelvis of the left kidney and all the papillae were necrotic. Histological examination showed considerable cellular infiltration of the demarcation zone, sclerosis of the arteries and arterioles, slight intercapillary glomerulo-sclerosis and thrombosis of some veins in the medulla of the kidneys.

*Case 2 (Ref. No. 8139/48):* A man of 74 suffered from a psychosis for more than 25 years. Diabetes was diagnosed in 1940, but did not need insulin. He was very thirsty and suffered from nocturnal frequency which had become worse during the last few weeks. There was considerable glycosuria. He had dietetic treatment, had suffered from lassitude and was confined to bed for a fortnight. On admission to Ullevål Hospital on April 11th, 1948, he was drowsy and unconscious. Temperature 36.5° C. Blood pressure 160/100 mm Hg. falling to 130/100. The bladder was distended up to the level of the umbilicus. Dribbling incontinence. The prostate was slightly enlarged but without nodules. During the first few days in hospital he had to be catheterized and there was no pyrexia, but on April 16th the temperature rose, and on April 19th it was 39.9° C. It fell slowly later on. The patient was apathetic and did not eat much and drank only little. Retard insulin was given, at first 32 + 24 units and later 40 + 32. The blood sugar varied between 120 and 462 mg %. There was ketonuria on admission which subsided later on. The amount of urine varied from 1,000 to 2,700 ml. On April 11th the urine contained no protein, but later on there was about 0.25 ‰. On April 13th microscopic examination of the urine showed a normal sediment, but on April 21st there were round cells and numerous rod-shaped micro-organisms, but further bacteriological examinations were not made. On April 11th the blood urea was 125 mg %. On April 13th, non-protein nitrogen was 84 mg %. W. R. was negative. On April 12th hemoglobin was 111 % and leucocytes 16,200. He died on April 28th.

Autopsy showed bilateral broncho-pneumonia. The kidneys together weighed 390 g. The right kidney was slightly enlarged and adherent to the perirenal fat. The capsule was easily detached, the surface was slightly granular. The cut surface showed necrosis of the renal papillae which did not extend to the cortex nor along the columns of Bertin. One papilla clearly had sloughed off, and this process had commenced in 2 other papillae which were partly detached from the rest of the kidney. The necrotic papillae were yellowish-white and were of a comparatively soft consistency. There was no inflammation of the renal parenchyma. Some gaping, thick-walled arteries were seen. The left kidney showed no evidence of inflammation, no abscesses, no necrosis of the papillae. The renal pelvis was enlarged on both sides and there were signs of severe cystitis.

*Histological sections of the right kidney* showed necrosis of the papillae (Fig. 4) and many micro-organisms both inside and outside the renal tubules, some of which were dilated. On the sides facing the columns of Bertin, the necrotic papilla showed a straight zone of dense cellular infiltration consisting of plasma cells, polymorphonuclear leucocytes and lymphocytes. Towards the cortex there was no such zone and the transition from necrotic to living tissues was not clearly defined. The capsule did not show any marked changes. Some glomeruli were hyaline and some were shrunken. Occasional slight intercapillary glomerulo-sclerosis was seen (Fig. 5). Fig. 6 shows the arteriolo-sclerosis. In several places the epithelium of the tubules is stripped off. The arteries showed moderate sclerosis. There were no thrombi in the veins and there was only slight inflammation of the renal parenchyma. There were some lymphocytes, but there was no sign of abscess formation.

*Summary.* A man of 74 suffering from psychosis and diabetes was admitted to hospital on account of his general condition and frequency of micturition which required catheterization. While in hospital he developed pyuria and fever. *Autopsy showed necrosis of all the papillae of the right kidney.* There was slight pyelonephritis. Histological examination showed intercapillary glomerulo-sclerosis and arteriolo-sclerosis.

*Case 3 (Ref. No. 5836/48):* A man of 80 had retention of urine in the autumn of 1944 and then developed frequency of micturition and the stream became smaller. He was admitted on February 19th, 1945, for recurrent retention of urine. Suprapubic cystostomy was performed and a de Pezzer's catheter was introduced. The prostate was enlarged, but firm and elastic. Diabetes was diagnosed and he was put on a diet and given 20 + 20 units of ordinary insulin daily. He was again admitted in the following August. The dose of insulin had been reduced because of hypoglycemic symptoms. It was now discontinued altogether, and there was no glycosuria or proteinuria when he was discharged. The urine was not examined microscopically.

On re-admission on March 12th, 1948, the blood pressure was 160/90 mm Hg. Intravenous urography on March 18th showed poor excretion on the right side. Suprapubic prostatectomy was performed on the following day under general anesthesia. The prostate weighed 100 g. The patient was exhausted after the operation and very listless. The blood urea was 45 mg% before the operation, but by April 11th, it was 192 mg%. A permanent catheter was introduced 18 days after the operation. Apart from post-operative pyrexia the evening temperature was 37.3° C to 37.7° C. On April 4th, there was a rise of temperature to 39.7° C and a rigor. The urine was alkaline with a specific gravity of 1.017 and contained protein, some leucocytes and rod-shaped bacteria. The sedimentation rate rose from 57 to 192 mm. He died on April 12th.

At autopsy the kidneys together weighed 300 g. The renal capsule stripped off easily and the surface of the kidneys showed several scars. Several papillae in both kidneys showed superficial necrosis. The renal pelvis on both sides was full of urine and pus. On the right side there were several small, yellow stones. The mucous membrane of the bladder was injected and thickened and partly gangrenous.

Histological sections showed superficial necrosis of the renal papillae. The narrow zone between necrotic and living tissue consisted of degenerate plasma cells, lymphocytes and polymorphonuclear leucocytes. Some glomeruli were hyaline or some were shrunken and the tubules showed advanced post-mortem changes. Elsewhere the kidneys showed moderate infiltration with various kinds of inflammatory cells. A thrombus was in a vein, blocking it almost completely.

*Summary.* A man of 80 was suffering from diabetes, and after an operation in 2 stages for hyperplasia of the prostate, he developed pyuria and hyperpyrexia with rigors. *Autopsy showed necrosis of several renal papillae in both kidneys, severe pyelonephritis and small stones in the right renal pelvis.* Histological examination showed considerable inflammatory changes and a thrombus in a vein.

*Case 4 (Ref. No. 24854):* A woman of 74 had an operation for prolapse of the uterus in 1941. Since 1942 she was treated at Ullevål Hospital for rheumatoid arthritis. The urine was normal, and the blood pressure was 145/90 mm Hg. On re-admission on November 26th, 1947, her blood pressure was 150/90, and there was no fever, but incontinence of urine. On the evening of February 8th, 1948, the temperature rose to 40° C and the patient had rigors. Next day she was very exhausted, her complexion was pale grey and she groaned feebly as she lay in bed. The urine was normal. On February 11th she complained of pain in the abdomen and of tenderness on pressure over the left iliac fossa. The temperature subsided with treatment with penicillin and it was discontinued on February 14th, when the abdominal pain disappeared. Blood culture on February 10th grew *Proteus*. After February 12th examinations of urine showed protein and numerous leucocytes. Bacteriological examination revealed *Proteus*. Apart from a few short periods without fever she had temperature until she died on April 29th.

Autopsy showed bilateral pleural effusion and right-sided bronchiectasis, acute fibrinous pericarditis, mitral regurgitation, congestion of the liver and spleen and cholecystitis with a stone the size of a nut in the gallbladder. The kidneys together weighed 280 g. The capsule was easily detached from the right kidney which had a patchy surface. There were altogether 4 small stones in the lower main calyx. Two papillae showed necrosis which extended to their bases. The adjacent tissue was dark blue. A third papilla had apparently sloughed off, leaving a necrotic patch. The papillae in the lower part of the pelvis were dark blue. There was considerable injection of the renal pelvis and its mucous membrane was dark. The papillae of the *left kidney* showed no necrosis but were dark. There was a small stone in the renal pelvis where the mucous membrane was inflamed. The mucous membrane of the bladder was inflamed and partly gangrenous.

*Histological sections of the right kidney* showed necrosis of the papillae with inflammatory changes near the necrosis as in the first case. The polymorphonuclear leucocytes, plasma cells and lymphocytes were degenerate. Part of one papilla was almost sloughed off. There was moderate arteriosclerosis with thickening of the intima. A large vein was partly obstructed by a thrombus. Many glomeruli were hyaline and some were shrunken. The tubules showed post-mortem changes. Many were stripped of their epithelium and some were dilated. In the interstitial tissue there were foci of plasma cells, polymorphonuclear leucocytes and lymphocytes. *Proteus* was recovered from splenic and renal tissue

*Summary.* A woman of 74 had incontinence of urine and rheumatoid arthritis. While in hospital she developed pyuria and fever. *Proteus* was recovered from both blood and urine before death. Autopsy showed pyelonephritis with stones in both kidneys and necrosis of two papillae in the right kidney. There was marked inflammatory infiltration in the kidneys, arteriosclerosis and thrombosis of a vein. *Proteus* was recovered from spleen and kidneys.

*Case 5* (Ref. No. 15519/48): A woman of 65 had rheumatic fever at the age of 11 and in 1911 diabetes was discovered. She was given dietetic instructions and insulin. She was admitted to Ullevål Hospital in 1947 for impending diabetic coma, and discharged with a daily dosage of 56 units of Retard insulin.

In July 1948, she had fever and shivering attack and on July 14th she was admitted to Ullevål Hospital in impending coma with deep respirations and fever. The urine contained sugar and ketone bodies. While in hospital, she had bouts of fever up to 40° C and several rigors. Insulin was given. The urine contained many leucocytes and bacteria; and *E. coli* was found several times. Sulphadiazine had no effect and the bacteria were insensitive to streptomycin. On August 27th urography showed opacities in the left kidney suggesting a stone. Ophthalmoscopic examination showed tortuous arteries and narrowed veins. She suddenly deteriorated and her temperature rose to over 40° C; she developed bed sores and died on October 2nd, 1948.

Autopsy showed pleural adhesions, bronchopneumonia, extensive arteriosclerosis and gallstones. The left kidney was much enlarged and the perirenal fat was edematous and the capsule was thickened. The surface of the kidney was dark, with a few yellow patches. The renal parenchyma was soft. The kidney and ureter were removed in continuity. Retrograde pyelography (Fig. 7) showed an ablong cavity in the upper pole of the kidney in connection with the upper calyx, which was nearly as thick as the little finger. The 2 other small upper calyces were dilated to about the size of a nut. The median and lower calyces were normal. On section the upper pole of the kidney contained a cavity which was nearly as large as a walnut and was connected with the renal pelvis. It was full of purulent urine. The wall of this cavity consisted of granulation tissue. In the position of another small calyx, a smaller cavity occupied the place of a papilla and communicated freely with the renal pelvis. The medullary rays converged towards and ended in this cavity (Fig. 8). There were no abscesses in the renal substance.

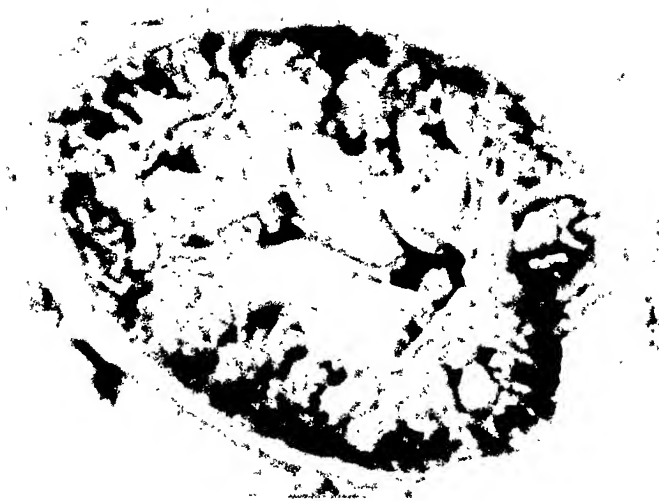
The right kidney was also enlarged and the cortico-medullary junction was blurred. The left ureter was thickened and dilated and the mucous membrane of the bladder was injected. The urine was cloudy. A blood culture taken after death yielded *E. coli*.

*Histological sections of the left kidney* showed thickening of the capsule, extensive hyaline change of the arterioles and partly hyaline and some degenerate glomeruli. There were considerable post-mortem changes in the tubules, but no arteriosclerosis. The papillae had apparently sloughed off and along the demarcation line there was an infiltration with plasma cells and some lymphocytes, but no polymorphonuclear leucocytes. There was necrotic tissue at the base of the sloughed-off papilla. In the renal parenchyma there were scattered foci of plasma cells. There was no definite abscess formation nor intercapillary glomerulo-sclerosis.

*Histological sections of the right kidney* also showed patchy infiltration with plasma cells and extensive sclerosis of the arterioles, but no necrosis of the renal papillae.

*Summary.* A woman of 65 suffering from diabetes was admitted to hospital almost in coma and with an infection of the urinary tract. Culture of the urine yielded *E. coli*. She died with signs of sepsis and high fever. *Autopsy showed that the upper papillae of the left kidney had sloughed off and that the adjacent renal tissue had been destroyed and cavities had formed.* Pyelonephritis was severe. Histological examination showed arteriosclerosis. Post-mortem blood culture yielded *E. coli*.

*Case 6* (Ref. No. 13719/48): A woman of 68 suffered from biliary colic and rheumatic fever. Between May 6th and October 11th, 1946, she was treated at Ullevål Hospital where hypertension (blood pressure 260/140 mm Hg.) and hypertrophy of the heart were discovered. She was given insulin for diabetes. Pyuria improved with sulphathiazole. Ophthalmoscopic examination showed no definite retinal changes. She remained comparatively fit till the spring of 1948, and she was admitted to Ullevål Hospital on June



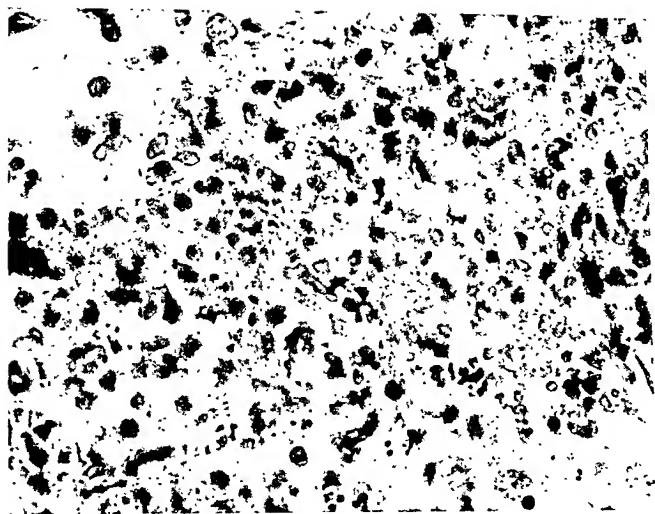


Fig. 3. Case 1. «Degenerate» leucocytes in the demarcation zone. (Hematoxylin and eosin,  $\times 700$ .)

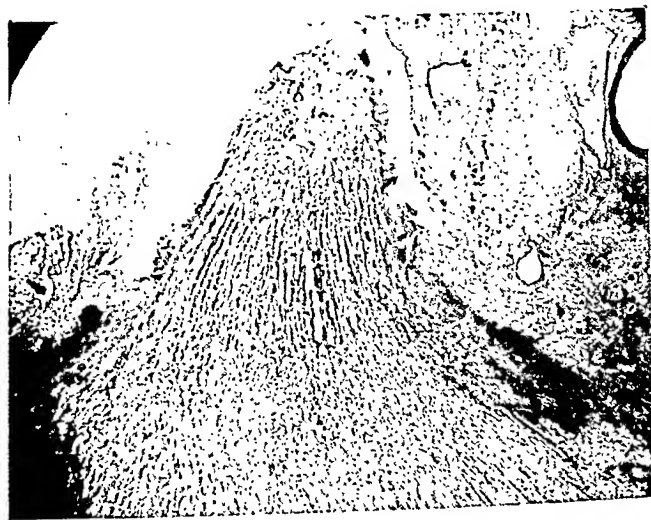


Fig. 4. Case 2. A necrotic papilla. The leucocyte demarcation zone, which is dark, is seen beside the columns of Bertin, but in the centre, towards the cortex, it is missing. (Hematoxylin and eosin,  $\times 10$ .)







Fig. 7. Case 5. Retrograde pyelography (post-mortem). Destruction of the parenchyma of the upper pole of the kidney with the formation of a large cavity which communicates with the renal pelvis.



Fig. 8. Case 5. A papilla has been sloughed off and a cavity has formed with a free communication with the renal pelvis. ( $\times 3.5$ .)

19th when the urine contained much sugar and a few cells, but no ketone bodies. She was not cooperative. Insulin was given, but its dosage was difficult to fix. On June 23rd and October 1st, 1948, *Proteus* was grown from the urine. The sedimentation rate was very high, 125 mm on June 21st, and 135 mm on October 11th. She died on October 23rd, 1948.

Autopsy showed fibrosis of the myocardium and atheromatous changes in the coronary arteries. There were 4 stones in the gallbladder. The right kidney was considerably enlarged and weighed 220 g. The perirenal fat was edematous and the capsule was thickened and somewhat adherent. The kidney was soft. Its cut surface showed that all the renal papillae were greyish-white, standing out in marked contrast to the rest of the kidney. The papillae showed necrosis which extended a little towards the renal cortex but did not reach it. In the upper pole of the kidney there was a tumour the size of a small orange. It was very soft and had a spotty, yellowish red appearance. The renal pelvis was dilated and the mucous membrane was injected; it contained turbid urine. The parenchyma of the kidney elsewhere was grey, without definite abscess formation.

The left kidney was small and weighed 120 g. Its pattern was blurred and the mucous membrane of the renal pelvis was inflamed.

*Histological sections of the right kidney showed necrosis of the papillae.* In the tubules in the necrotic area were many bacteria. The necrotic tissue was defined towards the cortex by a zone of infiltration consisting of degenerate round cells. The partly hyaline glomeruli showed degenerative changes and were shrunk and the number of cells and the amount of connective tissue in the capillary network was increased. There was no sign of arteriolosclerosis, but the tubules were degenerate. There was sclerosis of the arteries and the veins contained several thrombi. The mass in the upper pole was a Grawitz tumour. Lymphocytes and plasma cells formed scattered foci in the interstitial tissue. There were only few polymorphonuclear leucocytes.

*Summary.* A diabetic woman of 68 was admitted to hospital suffering from pyuria. *Proteus* was grown from the urine. *Autopsy showed necrosis of all the papillae of the right kidney.* There was advanced pyelonephritis and a Grawitz tumour was found in the upper pole of the kidney.

In all 6 cases of acute necrosis of the renal papillae described, the patients suffered from infection of the urinary tract, and 5 of them were diabetics. In the last 3 cases when our attention had been drawn to the condition, we suspected it on clinical evidence, but it was not diagnosed with certainty in life. Table I briefly presents the most important findings.

In 3 cases renal calculi were found on the same side as the papillary necrosis. The naked-eye appearance of the necrotic papillae was striking because of their yellowish-white colour which was in marked contrast to the rest of the kidneys. The necrosis involved the most prominent part of the papillae and did not extend to the cortex nor towards the columns of Bertin. In 1 case, the necrotic papillae had been discharged and there was destruction of renal tissue with cavity formation. In 5 cases with considerable pyelonephritis histological examination showed a marked cellular reaction near the necrotic area. In 1 case (No. 2) of slight pyelonephritis, there was marked infiltration in the areas near the columns of Bertin, whereas there was no cellular reaction in the direction of the renal cortex. The cells in the infiltrated areas were plasma cells and lymphocytes. Polymorphonuclear leucocytes were found in 4 cases and absent in 2. Most of the cells were degenerate and were difficult to identify. Among the 5 diabetics was only 1 with absence of

Table 1.

*Acute necrosis of renal papillae.*

Case	Age and sex	Pyelonephritis	Site of necrosis	Complicating diseases	Bacteriological findings
1	80, F.	Severe	Left kidney, all papillae	Diabetes, renal calculi	Proteus from blood and urine
2	75, M.	Slight	Right kidney, all papillae	Diabetes, retention of urine (fibrous prostate)	E. coli from renal tissue
3	80, M.	Severe	Both kidneys, all papillae	Diabetes, renal calculi, prostatectomy 3 weeks before	—
4	75, F.	Moderate	Right kidney, 3 papillae	Renal calculi	Proteus in blood and urine, and on culture from kidney and spleen (post-mortem)
5	65, F.	Severe, with cavity formation	Left kidney, all papillae partly discharged	Diabetes	E. coli from urine, from blood (post-mortem).
6	68, F.	Moderate	Left kidney, all papillae	Diabetes, Grawitz tumour	Proteus from urine

an inflammatory zone between necrotic and living tissue. In only 2 of the 5 diabetics there were many plasma cells but few polymorphonuclear leucocytes a feature which Edmondson et al. state is characteristic of the inflammatory infiltration in cases of acute necrosis of the papillae. With one exception the renal vessels showed arteriosclerosis. In Cases 1 and 2 there was also slight intercapillary glomerulosclerosis. In Edmondson's series glomerulo-sclerosis was frequent. In 4 of our cases thrombi were seen in the veins. Like other observers we found that most patients are elderly. The ages of our patients ranged from 65 to 80.

Infections of the urinary tract and septicemia with *Proteus* were noted in Cases 1 and 4. In Case 6 *Proteus* was grown from the urine. In Case 5 infection of the urinary tract was due to *E. coli*. The presence of this organism in the blood may have been a post-mortem change. In Case 2 bacteriological examination was only undertaken post mortem. Edmondson et al. pointed out that the infection was mainly due to staphylococci and *E. coli*, and only in one case was *Proteus* isolated on bacteriological examination of the kidneys after death. They suggested that the infection may start from an extrarenal focus or that the urinary infection may be the primary focus. When the primary focus is extrarenal, bacteremia occurs first and infection of the urinary tract comes from the blood stream. In none of our 6 cases was there any extrarenal focus, but in every case there had been infection of the urinary tract of variable duration before death. Our observations therefore suggest that a generalized septic infection often starts from the

urinary tract. The invasion of the blood stream takes place simultaneously with or after the development of necrosis of the papillae. In other words, the infection proceeds from the kidneys to the blood stream, but not in the reverse direction. The necrosis of the papillae therefore contributes directly to the generalized infection. In 4 of our cases histological examinations showed thrombi in the veins of the renal medulla. This finding suggests that an invasion of the blood stream from a focus of infection in the kidneys is not rare.

It is remarkable that in 2 of our cases septicemia was caused by *Proteus*. In a third case the urinary tract was infected with *Proteus* which possibly was also responsible for the generalized infection. It is very rare for *Proteus* to invade the blood stream. This organism is usually saprophytic, but it may also be pathogenic when it has a tendency to settle in the urinary tract, the ear or the intestinal tract. Its etiological importance in the diarrhoea of children, for example, is still in doubt in the opinion of most observers. With regard to infections of the respiratory tract, Dick Henriksen (8) (1937) stated that *Proteus* is not often responsible for them, but may occasionally cause serious trouble. Thjotta (9) and Iromonoiu and Popa (10) have described cases of *Proteus* septicemia with otitis media as the primary focus. Abrams (11) (1948) collected 52 cases of *Proteus* septicemia, and the primary focus was in the ear, nose or throat in 44.7 %, and in the urinary tract in 46.8 %. Most of the patients were acutely ill with fever and rigors, and the temperature curve in some of the cases was of the typhoid type. In 15 of the 22 cases in which the infection had started from the urinary tract the disease developed after an operation. Abrams reported a case in which penicillin had no effect, whereas streptomycin given in doses of 0.3 g 3-hourly for 10 days led to a cure. In a report by the *National Research Council* (12) reference is made to 94 cases of septicemia treated with streptomycin. Among them were 5 cases of *Proteus* septicemia, which recovered or improved. It is therefore possible that with streptomycin treatment the prognosis may improve also in cases of acute necrosis of the renal papillae. We did not have an opportunity to give streptomycin to any of our patients.

As pointed out acute necrosis of the papillae was not diagnosed definitely on clinical evidence in any of our cases. The clinical picture usually shows that patients suffering from diabetes and infection of the urinary tract become worse, with a rapid pulse, high fever and mental confusion. In all our cases where a blood-culture was taken it gave positive results. In 3 of our cases, the sedimentation rate was remarkably high, and in Case 1 it ranged from 120 to 105 mm, in Case 6 from 125 to 135 mm, and in Case 3 it rose from 54 to 192 mm.

### Summary.

Acute necrosis of the renal papillae is described in 6 patients suffering from infection of the urinary tract treated at the Ullevål Hospital during 1948. Five of the patients were diabetics and 3 of them had renal calculi on the affected side; one of them also had retention of urine. The sixth patient suffered from retention

of urine, but not from calculi. The ages of the patients ranged from 65 to 80 years. In every case the papillary necrosis was first diagnosed at autopsy. *Proteus* was isolated from the blood and urine of 2 patients and also from the urine of a third patient whose blood had not been examined. Necrosis of the papillae was unilateral in 5 cases and bilateral in 1. The renal vessels showed arteriosclerosis in 5 cases. In 3 cases of diabetes arteriolosclerosis was found, and in 2 of these cases intracapillary glomerulo-sclerosis was also present. In 5 cases there was a well marked zone of inflammation at the junction of necrotic and living tissue. In one case of diabetes this zone was absent. Many plasma cells but few polymorphonuclear leucocytes (alleged to be characteristic of the inflammatory infiltration occurring in diabetes with necrosis of the papillae) were seen in 2 cases, but not in the other 4. In one case the necrotic papillae had been eliminated with destruction of renal tissue and cavity formation suggesting renal tuberculosis when urography was undertaken post mortem.

The importance of adequate treatment of infections of the urinary tract is stressed. When necrosis of the renal papillae is unilateral, nephrectomy may be advisable.

#### References.

1. Edmondson, H. A., H. E. Martin and N. G. Evans: *Arch. Intern. Med.*, 79: 148: 1947. — 2. Friedreich, N.: *Virchows Arch.*, 69: 308: 1877. — 3. Günther, G. W.: *Münch. Med. Wschr.*, 84: 1695: 1937. — 4. Alken, C. E.: *Z. Urol.*, 32: 433: 1938. — 5. Mellgren, J. and G. Redell: *Acta Chir. Scand.*, 84: 439: 1941. — 6. Eskelund, V.: *Acta Radiol.*, 26: 548: 1945. — 7. Menkin, V.: *Arch. Path.*, 34: 182: 1942. — 8. Henriksen, S. Dick: "Studies on the flora of the respiratory tract". Oslo 1937. — 9. Thjotta, Th.: *Norsk. Mag. Lægevidensk.*, 77: 1443: 1916. — 10. Irimonoui, G. and R. Popa: *C. R. Soc. Biol. Paris*, 92: 1082: 1925. — 11. Abrams, H. L.: *New Engl. J. Med.*, 238: 185: 1948. — 12. Report from the National Research Council. *J. Amer. med. Ass.*, 132: 4: 1946.
-

From the Department of Medical Tuberculosis, St. Göran's Hospital, Stockholm.

## Observations Concerning the Presence of Pyogenic Staphylococci in the Nose and their Relationship to the Antistaphylolysin Titre.

By

SVEN BERGQVIST.

(Submitted for publication July 4, 1949.)

Several investigators (6, 7, 9, 10, 13, 14, 15, 21) have shown that wound infections, furuncles, the presence of staphylococci in operating theatres, etc. originate from the nose of staphylococcal carriers. This comprises 35—50 per cent of all healthy individuals. Mc Farlan (13) considered that most individuals were carriers at some time, but Miles et al. (14) demonstrated that there is striking constancy in the carrying of staphylococci. Packalén and Bergqvist (17) observed that high antistaphylolysin (ASta) titres occur more often in persons with staphylococci in the nasal mucosa than in non-carriers. The aim of the present investigation is to study the variations in the occurrence of staphylococci in the nose, and their relationship to variations in the ASta titre more closely.

*Bacteriological Technique.* Swabs were taken from both nostrils (vestibulae and nasal fossae) and immediately inoculated onto a blood agar plate containing 5 per cent horse blood and incubated aerobically for 18—24 hours at 37° C before subculture. The criterion of pyogenic staphylococci was taken to be the presence of a positive coagulase test. In two cases, however, hyaluronidase-producing and haemolysin-positive yellow staphylococci, constantly present in large numbers, were classified as pyogenic despite the fact that they were coagulase-negative. In one of these cases, however, the ASta titre rose appreciably during the observation period. The techniques employed in the performance of the coagulase test, the evaluation of pigment and the haemolysin test, are described in a previous paper (17).

*Serological Technique.* Specimens of blood for ASta determination were taken at least as often as specimens from the nose (see below). The titrations were performed in accordance with a method described earlier (17). Inactivated serum was kept in cold storage at — 20° C, thus permitting the simultaneous titration,

Table I.

*Incidence rates of elevated ASta-titres ( $\geq 1$  I. U.) in carriers and non-carriers.*

Nasal swab for <i>Staphylococcus pyogenes</i>	No. of Patients	ASta-titre $\geq 1$		Difference
Positive .....	60	37	62 $\pm$ 6.3 %	
Negative .....	69	18	26 $\pm$ 5.3 %	36 $\pm$ 8.2 %
	129	55	43 %	

when required, of all serum specimens from one patient, and thereby eliminating certain technical sources of error in the evaluation of possible rises or falls in the titre. Only those changes which amounted to at least double or to half the previous values were considered significant.

*Material.* Of the 129 patients examined, 109 were suffering from tuberculosis (pulmonary tuberculosis and/or exudative pleurisy), and all those, who were under observation for at least one month (81 cases) had this disease. In the majority of cases, the investigations were instituted on recently admitted patients, though in a small number only after some time in hospital. The specimens were taken at regular intervals of either 1 or 2 weeks, but when the patients had been discharged and the examinations were being performed at the out-patient clinic, the intervals might be as long as 1 or 2 months and in certain cases even longer.

Table II.

*Relationship between frequency of elevated ASta and AS-titres.*

ASta-titre	No. of patients	AS-titre $\geq 200$	
$< 1$ .....	74	32	43 %
$\geq 1$ .....	55	26	47 %
	129	58	45 %

Of all the patients examined — 47 men and 82 women — 60 (46.5 per cent) showed coagulase-positive staphylococci in the nose on first examination, and of these, 37 (62 per cent) had an ASta titre of  $\geq 1$  unit (Table I). Of the subjects in whom staphylococci were not demonstrated in the first specimen, titres of  $\geq 1$  unit occurred in only 26 per cent. The difference between these figures amounts to 36 and is more than four times the mean error of the difference.

Packalén (16) has shown that patients with haemolytic streptococci in the pharynx also presented a higher incidence of pyogenic staphylococci than those who had no streptococci. For this reason, high ASta titres might be expected to be associated with high antistreptolysin (AS) titres. And indeed, Tunevall (18) found a certain relationship between high AS titres and high ASta titres in school-children.

In Table II the titres have been correlated, but high AS titres did not occur appreciably more often among cases with high ASta titres than among those with





Table IV.

*Persistence of carriage and non-carriage of staphylococcus pyogenes.*

Observation periods in months	Persistently positive		Persistently negative	
	No. of patients	No. of swabs per patient	No. of patients	No. of swabs per patient
1—2.....	31	5	27	4
3—4.....	26	7.8	25	5
5—6.....	20	9.4	21	6.7
7—12.....	17	11	12	10.7
13—19.....	11	16	8	16.1

ward. If the cases were observed over a longer period (14 weeks) constantly positive findings occurred in 15—20 per cent and constantly negative ones in about 10 per cent.

In the present series the corresponding figures amount to 33 and 37 per cent respectively. Table IV shows the observation periods of these 58 patients, from whom a total of 518 swabs were taken. As will be seen, patients with negative findings were examined, hardly less often than those with positive findings, so that the absence of staphylococci in the negative group is not due to less thorough follow up. In previous investigations (16, 19, 20) it has been demonstrated that streptococci and staphylococci occur more abundantly in the pharynx and nose in tuberculous patients than in patients with other internal diseases, and that the AS and AS<sub>t</sub> titres are often elevated in the former. This probably explains why the percentage of constant carriers of staphylococci is larger here than in the series reported by Miles et al.

Although the number of staphylococcal carriers is comparatively large and the probability of infection is therefore appreciable, there are, nevertheless, individuals in whom staphylococci are constantly absent from the nose. It seems likely therefore, that there is present in the nasal mucosa of these individuals, a constitutional factor, anatomical or physiological in nature which is inimical to the existence of staphylococci. The presence of a growth-inhibiting factor in the nasal secretion seems the most plausible explanation, though it can scarcely be thought to consist of the lysozyme, first demonstrated by Fleming (3, 5, 8), which is present in large amounts in the nasal mucus.

In 13 cases (17 per cent) a rise in the AS<sub>t</sub> titre occurred during the observation period. In 6 of these, one of whom developed staphylococcal empyema, staphylococci were constantly found in the nose. Staphylococci appeared later on in 4 cases which were at first negative. In the other 3, surprisingly enough, no staphylococci were demonstrable at any time. This rather unexpected result suggests that staphylococci nevertheless existed somewhere within the system, though none were found at the site where they are most commonly encountered, *i. e.* the nasal mucosa, and no clinical evidence of staphylococcal disease could be demonstrated. Adamson's (1) frequent findings of staphylococci in lymph glands, showed how the bacteria from the mucosa invade the deeper regional glands *via* the lymph

channels. If they are not eliminated by the body defences, they will, of course produce toxin, while forming real foci of infection, with a consequent rise in the ASta titre. This contention is supported by Adamson's findings (2), viz. that a considerably higher proportion of those patients with staphylococci in the lymph glands had a more elevated ASta titre than those without; and also by the fact that many of the patients with staphylococci in the tonsils or the bronchi, but with sterile lymph glands, presented ASta titres less than 1 unit.

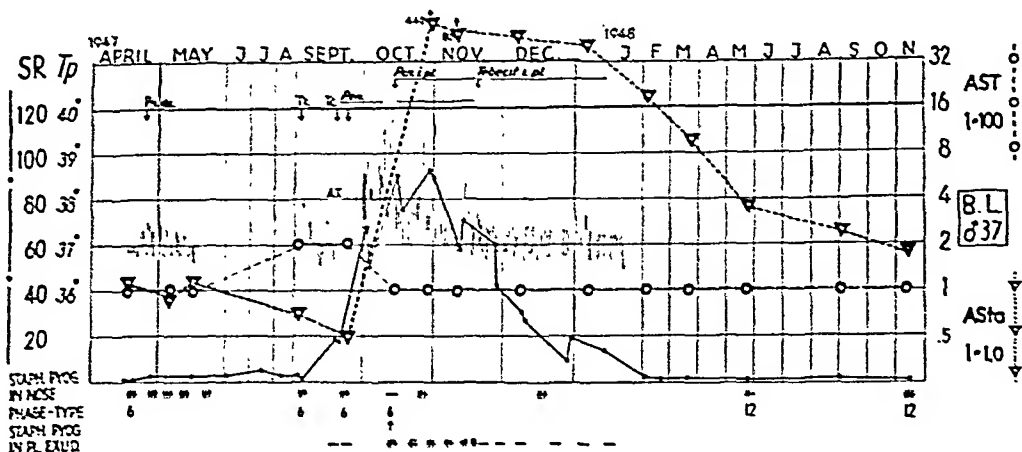


Fig. 1.

Growth of staphylococci: +++ abundant, ++ moderate, + sparse, — no.

### Followed-up Cases.

To illustrate the relationship between the finding of staphylococci, fluctuations in the ASta values and features of the clinical course, an account is given of some of the cases investigated. Fig. 1, for instance, shows a 37-year-old man with tuberculous cavities in the right lung, first treated by pneumothorax therapy (pn) and five months later thoracocautery (Tk). One week later the patient developed tonsillitis (A. T.) at the same time complaining of pain in the right side of chest. A pleural effusion was demonstrated and paracentesis (TC) performed. Although the effusion was found to be sterile, penicillin treatment was nevertheless instituted by the intramuscular route. A further pleural tap 2 days later still showed the effusion to be sterile. In spite of treatment with penicillin for 2 weeks, there was a persistent pyrexia, and repeated tapping disclosed the presence of an empyema caused by staphylococci of the same type (type 6), as those demonstrated in the nose on repeated examination. Tapping and irrigation of the pleural cavity were carried out daily, and instillation of penicillin in large amounts was combined with intramuscular injections; the staphylococci however rapidly became resistant to penicillin. Irrigation of the pleural cavity with tebecit was therefore started, and on the following day the pus was sterile. In the meantime the ASta titre rose to exceptionally high values (440 units), but gradually subsided to as low as 1.5 units. The staphylococci disappeared from the nasal mucosa after the initial treatment with penicillin, but returned during the second period of treatment. This time, however, they were of another type (type 12). During the further course of the disease the AS titre was not influenced.

The second case (Fig. 2) is that of a 34-year-old woman with tuberculosis of the left lung, who received pneumothorax therapy from July, 1947 onwards. During the first month no staphylococci could be demonstrated in the nose, and the ASta titre was low.

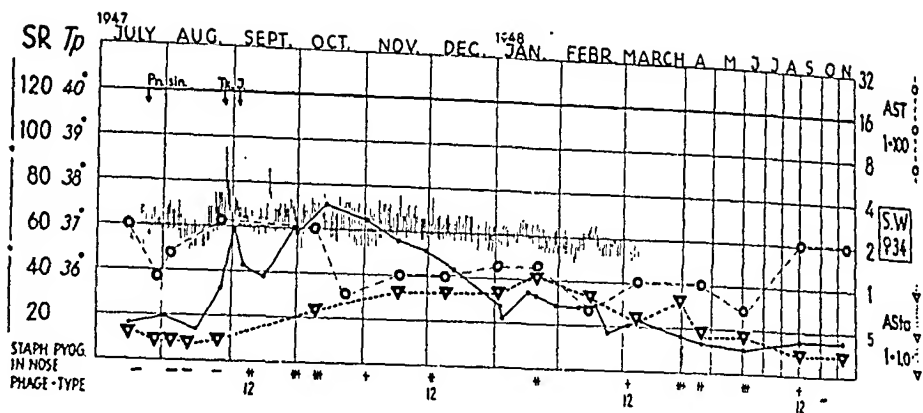


Fig. 2.

But early in September, some days after a thoracocautery, the patient had a recurrence of polyarthritides (J) with a rise in the sedimentation rate. Type 12 staphylococci were demonstrated in the nose at about the same time, and were subsequently found in all swabs. The ASSto titre gradually rose and reached its highest value 4 months after the date when staphylococci were first demonstrated, and subsequently subsided. Moderate variations in the AS titre are in no way related to the ASSto titre.

Fig. 3 shows a case of bilateral pulmonary tuberculosis in a 22-year-old man, where pneumothorax was instituted first on the left and subsequently on the right side. During the first few months no staphylococci were found in smears from the nose, and the ASSto titre was low — 0.5 units. On hospitalization for the third time, staphylococci were demonstrated in virtually pure cultures from the nose, these findings being repeated at each examination. No influence on the ASSto titre could be observed. In this case the staphylococci probably did not invade the lymph glands, and in any case did not give rise to the formation of antibodies.

In a 22-year-old woman (Fig. 4) with a tuberculous lesion in the right lung, pneumothorax therapy was instituted towards the end of March, 1947. Six months later lesions developed in the other lung, and the patient was re-admitted for bilateral pneumothorax treatment. Throughout the observation period no yellow staphylococci could be found in any swab from the nose. The ASSto titre, which during the first few months remained at about 0.5 units, rose to a very high level — about 10 units — during an exacerbation in the left lung demonstrated by X-Rays. The patient otherwise showed no subjective or objective signs whatsoever of the staphylococcal infection. Subsequently the ASSto titre fell to normal values during the course of a year.

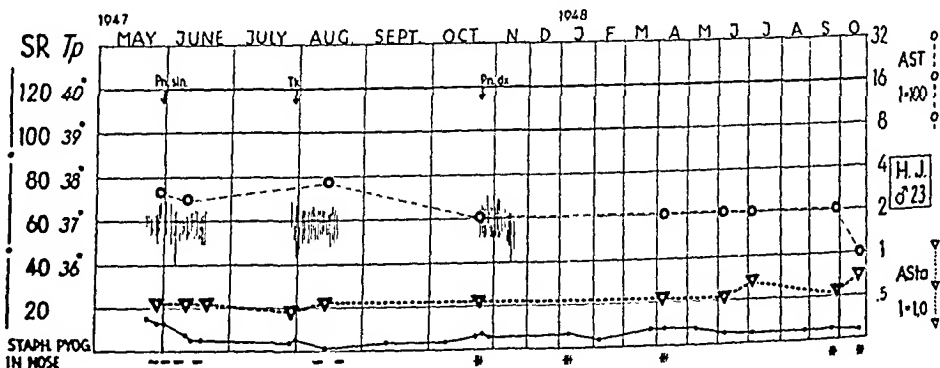


Fig. 3.



a connection between those changes and subjective or objective symptoms in the patient (cf. the investigations of Westergren and Stavenow; 19, 20). We do not know as yet whether the staphylococci ought to be followed with the same interest as has long been devoted to the haemolytic streptococci, but there is at least a possibility of their being of greater significance than thought hitherto.

### Summary.

In a series of 129 patients, most of whom suffered from pulmonary tuberculosis, a definite relationship was observed between the findings of pathogenic staphylococci in the nose and a high antistaphylolysin titre (ASta). 81 of these cases were investigated by repeated tests over periods varying between one month and one and a half years and staphylococci were regularly demonstrated in the noses in 33 per cent, but were absent in 38 per cent. An increased ASta titre was present in 63 per cent of those in the constantly staphylococcus-positive group, but only in 16 per cent of those in the constantly negative group.

In 13 patients a rise in the ASta titre was observed: but only in one of these was it possible to demonstrate clinical evidence of staphylococcal infection. In three of them no staphylococci were found in the nose. The reason for the increased titres in these cases is discussed.

The expenses of this study were defrayed by grants from the National Anti-Tuberculosis Association of Sweden.

### References.

1. Adamson, C.-A.: *Nord. Med.*, 33, 138 (1947). — 2. Adamson, C.-A.: *Acta Med. Scand.*, Suppl. 227 (1949). — 3. Andersson, H.: *Arch. Otolaryng.*, 20, 38 (1934). — 4. Baber, M.: *J. Path. Bact.*, 59, 373 (1947). — 5. Daly, S.: *Arch. Otolaryng.*, 27, 189 (1938). — 6. Danbolt, N.: »Undersøgelser over Stafylokokker med særlig henblik på furunkulosens epidemiologi.» Oslo, 1932. — 7. Devenish, E. A., and Miles, A. A.: *Lancet*, I, 1088. (1939). — 8. Fleming, A.: *Proc. Roy. Soc.*, 93, 306 (1922). — 9. Gillespie, E. H., Devenish, E. A., and Cowan, S. T.: *Lancet*, II, 870 (1939). — 10. Hart, D.: *Arch. Surg.*, 34, 874 (1937). — 11. Laurell, G.: In press. — 12. Mc Clean, D.: *Biochem. J.*, 37, 169 (1943). — 13. Mc Farlan, A. M.: *Brit. Med. J.*, II, 939 (1938). — 14. Miles, A. A., Williams, R. E. O., and Clayton-Cooper, B.: *J. Path. Bact.*, 56, 513 (1944). — 15. Moss, B., Squire, J. R., Topley, E., and Johnston, C. M.: *Lancet*, I, 320 (1948). — 16. Packalén, Th.: *Nord. Med.*, 31, 2014 (1946). — 17. Packalén, Th., and Bergqvist, S.: *Acta Med. Scand.*, 127, 291 (1947). — 18. Tunevall, G.: *Acta Pædiat.*, 35, 232 (1948). — 19. Westergren, A.: *Acta Med. Scand.*, Suppl. 213, 323 (1948). — 20. Westergren, A., and Stavenow, S.: *Ibid.*, Suppl. 196, 545 (1947). — 21. Williams, R. E. O., *J. Path. Bact.*, 58, 259 (1946).

From the Medical University Clinic at the City Hospital of Aarhus, Denmark.  
(Director: Professor, Dr. med. C. Holten.)

## Treatment with Dicumarol in Small Continuous Doses.

By

LEOPOLD EPSTEIN and ASGER NØRHOLM—PEDERSEN.

(Submitted for publication July 7, 1949.)

Since dicumarol (3-3' methylen bis (4-hydroxycoumarin) = »Synparin» (was used first in 1941 in anticoagulant therapy (2, 5, 8) intermittent application has been most frequently used. Treatment is begun with 50 to 75 centigram (cg) of dicumarol by mouth, the effect of this initial dose on the prothrombin time is observed and treatment is then continued while daily readings of the prothrombin time are made. The characteristic feature of the treatment lies in the large maintenance doses, frequently 25 cg dicumarol every time and the long intervals (often several days) between the doses. It is common experience (fig. 1) that this dosage makes it difficult to maintain the prothrombin time in what is considered as a therapeutically active zone. Variations frequently occur in the prothrombin index and the purpose of the treatment, which is the constant reduction of the coagulation of blood, is not maintained, or the danger of bleeding arises. Variations in the prothrombin index are particularly obvious when anticoagulant treatment is continued for a long period.

Another form of dosage was therefore tried and it was hoped that it will provide easier maintenance of the prothrombin index in the therapeutically effective zone. In the literature little information is available regarding the forms of dosage other than the intermittent one which is generally used. Meyer, Bingham and Axelrod (1942) recommended after an initial dose of 5 mg per kg of bodyweight small daily doses of 1.5 mg per kg. Their series comprises 14 patients, 10 of whom were treated for 8 days. In other cases the treatment was continued longer, but could not be carried to its conclusion on account of a considerable rise in the prothrombin time. The maintenance dosage was probably too high. Bingham, Meyer and Howard (1943) who also reported a small series believed that a more constant level of the plasma prothrombin can be obtained by the daily admini-

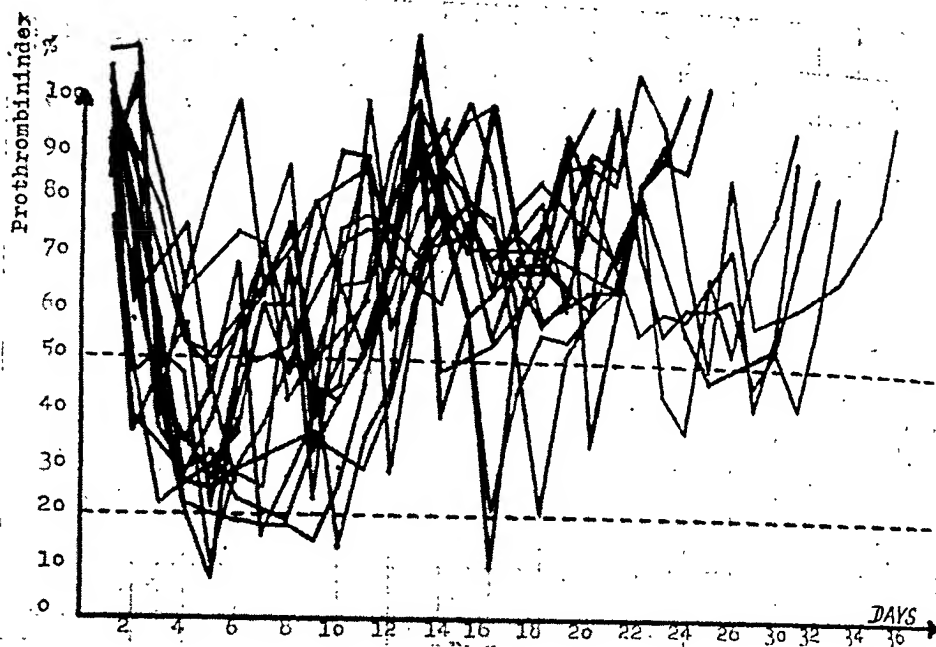


Fig. 1. 15 patients with coronary thrombosis treated with large intermittent doses. Note the large fluctuations. The prothrombin index could not be maintained in the therapeutically effective zone between index 20 and 50.

stration of a small dose (1.5 mg per kg) than by intermittent dosage. Jansen (1944) used daily dosage in 4 cases, all of whom received 12.5 cg from the start. The experiments were of short duration: 6, 7, 7 and 12 days. In all cases a steady rise in the prothrombin time occurred. Jansen reached the conclusion that it is not easily possible to find a dosage which produces a constant reduction of the prothrombin index. Bruzelius (1945) stated that Lehmann tried small daily dicumarol doses for the prophylaxis against postoperative thrombosis. In the beginning 5 cg were given twice daily and then 5 cg daily for 3 days. The prothrombin index fell slowly to between 40 and 60 until the 5th—7th day and then it was again allowed to rise. The advantages of this regime are not obvious, however, because of the short time of treatment.

*The purpose of this investigation was to find a method of dosage which might make it possible for the prothrombin index to be maintained within the therapeutically effective zone. Opinions differ somewhat about the level of this zone. Allen, Barker and Waugh (1942) recommended an index between 30 and 60. Bingham, Meyer and Howard (1943) considered a zone between 50 and 65 as suitable. Lehmann (1943) gave an index between 20 and 60 in the treatment of thromboses and between 30 and 60 for prophylaxis. Bruzelius (1945) recommended an index between 30 and 60 in the treatment of thromboses and between 40 and 60 for prophylaxis. On the basis of this experience we chose a zone between 20 and 50 for the prothrombin index, as this zone represents a therapeutically effective reduction of the prothrombin contents and at the same time does not involve the risk of serious hemorrhage.*

### Our Investigations and Results were as follows:

The series comprised 37 patients and their diagnoses are given in table I. Apart from 4 patients with disseminated sclerosis there was no question of treatment of thrombosis or prophylaxis as regards the other cases. It may therefore be regarded as a selection of normals.

The prothrombin index was determined according to Lehmann's method (1941) by taking citrated blood as for the sedimentation rate. The blood tests are practically always taken between 7 a. m. and noon before the main meal of the day.

Continued vomiting and diarrhoea necessitated the interruption of the treatment in one case after the 6th day; 2 patients were discharged at an early stage after the 5th and 7th day. Hemorrhage caused by the treatment was observed in 2 cases only. In one case intestinal hemorrhage occurred after 12 days' treatment; the prothrombin index was then 29 and treatment with synparin was immediately discontinued. In the other case hematuria occurred when the prothrombin index was 22. The treatment was stopped for some days until hematuria had ceased and was then continued with a smaller daily maintenance dose.

### Methods of Dosage.

Three methods of dosage were investigated. At the beginning 25 cg synparin is given and on the second day the same dose or two smaller doses morning and evening (*e. g.* 12.5 + 12.5 cg, or 12.5 + 6.25 cg), and the same dose on the 3rd and 4th day, so that on the first 2—4 days up to 72 cg are given before the therapeutic zone is reached. The evening- and following morning dose for each day were not fixed until the prothrombin index was calculated. Where the index was between 30 and 60, 6.25 cg synparin was given daily, and the same dose was given twice daily when the index was about 50, especially when there was a tendency to rise. With more pronounced rises, 6.25 cg + 12.5 cg was given daily. With index figures below 30 the treatment was temporarily discontinued in order to await a rise to the average figure for the therapeutically effective level and then treatment was resumed. Experience showed that the rise is often much greater than intended. Tablets of 25 cg were used. For practical reasons the doses were therefore 12.5 cg or 6.25 cg. The maintenance doses were smaller than with the usual intermittent dosage, but large compared with the amount used in continuous dosage.

This method was used in 16 cases. Figs. 1 and 2 show that this method gives better results than intermittent dosage with large doses, but the necessity of awaiting the daily prothrombin determinations before the fixation of the dose, and the fact that intervals of one or more days may become necessary makes the method somewhat similar to the original intermittent dosage. The possibility was therefore considered of obtaining an even and steady reduction of the prothrombin time by the following modification: (1) the single doses were smaller, (2) the doses were spread more evenly throughout the day so as not to be forced





**Table I.**  
*Patients Investigated.*

Diagnosis	Number of patients
Nervousness, neuroses .....	17
Sciatica or myalgia .....	6
Disseminated sclerosis .....	5
Chronic constipation .....	2
Asthenia .....	1
Obesity .....	1
Arthritis of hip joint .....	1
Parametritis .....	1
Epilepsy .....	1
Bronchitis .....	1
Senile dementia .....	1
Total	37

**Table II.**  
*Initial Dose in Centigram for Obtaining the Therapeutically Effective Level.*

Centigram	Number of cases
10—19 .....	1
20—29 .....	2
30—39 .....	3
40—49 .....	2
50—59 .....	16
60—69 .....	10
70—79 .....	1
80—89 .....	1

**Table III.**

*Number of Days during which the Maintenance Dose Was Given after the Desired Level Was Reached.*

Days	Number of cases	
	I	C
5—9 .....	3	4
10—19 .....	8	4
20—29 .....	5	4
30—39 .....		3
40—49 .....		1
50—59 .....		
60—69 .....		
70—79 .....		1
Total	16	17

**Table IV.**

*The Daily Average Maintenance Dose in Centigram in Relation to Level of Bodyweight.*

Centigram	Thin	Average	Stout
3—3.9 .....	2	2	
4—4.9 .....	1	2	
5—5.9 .....	1	4	2
6—6.9 .....	3	6	2
7—7.9 .....	2	4	
8—8.9 .....	1	1	
9—9.9 .....		1	
Total	10	20	4

3 Cases not included on account of early cessation of the treatment.

I: Intermittent treatment with small doses.

C: Continuous treatment.

(4 cases not included on account of early cessation of the treatment.)

indicated for the 16 patients who were treated with continuous small doses. In Fig. 2 the curve is satisfactory in 6 cases only, whereas Fig. 3 shows a satisfactory curve in 14 cases. In one case the continuous treatment produced a steady curve, but it is not shown in Fig. 3 because it was outside the therapeutically effective level. An initial dose of 50 cg did not produce this effect. We did, however, want to see if a small continuous maintenance dose could maintain the level reached. This proved to be possible with 2 cg synparin three times daily. After 18 days of treatment a supplementary dose of 12.5 cg was given and the prothrombin index was brought down to 50. The prothrombin index was then maintained at the new level for 10 days. In a patient where the curve with continuous dosage was unsatisfactory, it was necessary to discontinue synparin because of hematuria; the prothrombin index rose therefore above the therapeutically effective level and the treatment was resumed with a smaller dose

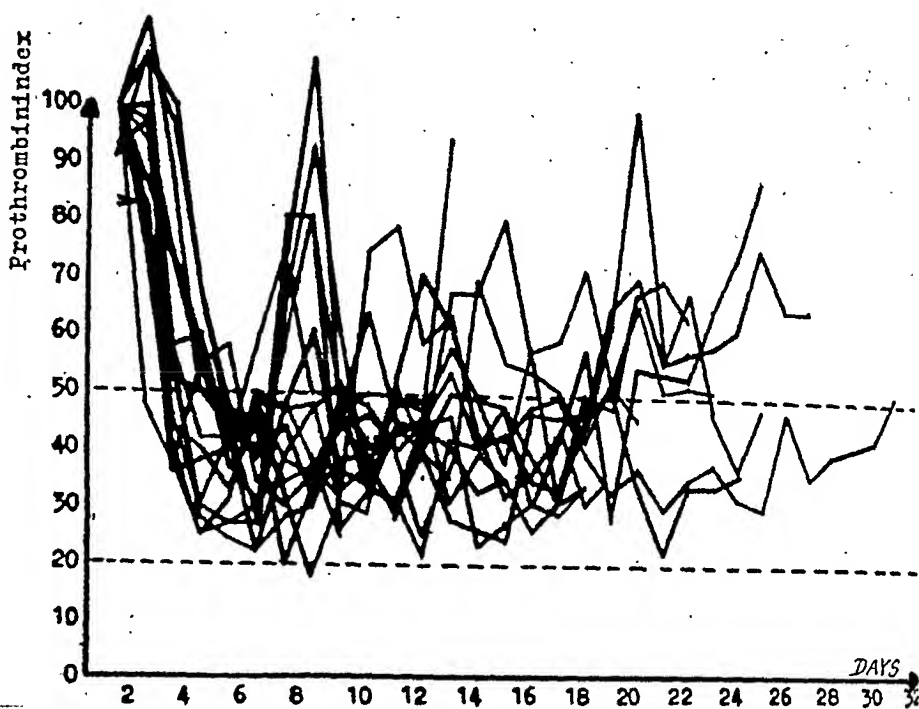


Fig. 2. 16 patients of the present series treated intermittently with small frequent doses. The prothrombin index is maintained better in the therapeutically effective zone than by treatment with large intermittent doses. The curve is only satisfactory in 6 patients.

(the curve outside the therapeutically effective level in Fig. 3 is indicated with a dotted line).

If we compare the large fluctuations in the prothrombin index with the usual big intermittent doses (Fig. 1) and the even curve in continuous dosage the difference is striking. The fluctuations of the prothrombin index in continuous dosage with small doses distributed over the whole day are always even, and as a

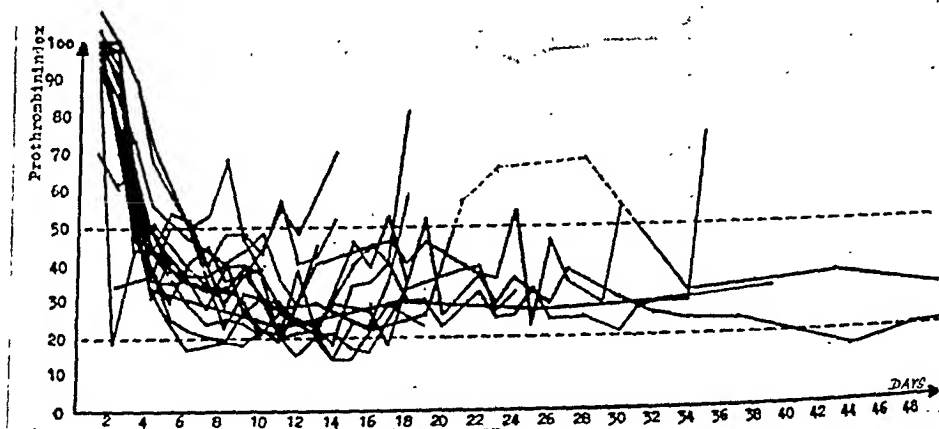


Fig. 3. 16 patients of the present series treated with small continuous maintenance doses. The fluctuations of the prothrombin index are small. The curve was satisfactory in 14 patients.

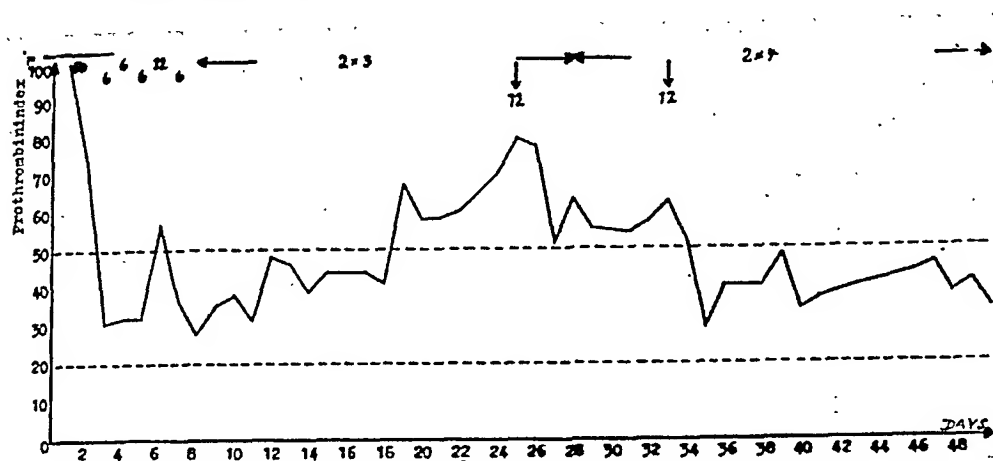


Fig. 4. Prothrombin index from a patient treated with small continuous maintenance doses. The curve is not satisfactory, but the small fluctuations are even. The rise in this case is controlled by a small supplementary dose. (The figures above the curve indicate the dose in centigram.)

rule they can be overcome by altering the dose, possibly by discontinuing synparin for 24 or 48 hours. In one case the prothrombin index rose steadily above the desired level (Fig. 4); a supplementary dose of 12.5 cg brought down the prothrombin index to approximately 50, but the daily maintenance dose had to be increased to 2 cg four times daily. As the level was still above a prothrombin index of 50, the dose was increased by a further 12.5 cg. The curve then remained at a prothrombin index of 30 to 50 for 17 days.

A great advantage of the continuous treatment is also that the daily reading of the prothrombin time is not absolutely necessary because the prothrombin index varies only slightly from day to day. On the other hand anticoagulant therapy with large intermittent synparin doses can only be carried out when the prothrombin time is controlled by daily readings. This makes continuous treatment more convenient for the patient and means a simplification of hospital work. The patient can be treated as an outpatient with a better margin of safety. It seems that the daily treatment with small doses causes fewer subjective discomforts, such as dyspepsia, than a few big intermittent doses.

### Summary.

The dosage of dicumarol (synparin) which is frequently used in thrombotic or embolic cases in large intermittent maintenance doses often produces considerable fluctuations in the prothrombin index.

A more constant reduction of the prothrombin index is desirable. In 37 patients without thrombotic phenomena other methods of dosage were tried. The best results were obtained with small maintenance doses of 2 centigrams two to four times daily, depending on the individual response. In 14 out of 16 patients treated a satisfactory reduction of the prothrombin index was obtained to the desired level between 20 and 50.

An advantage of this method is that fluctuations in the prothrombin time are small, and are easily controlled by a slight alteration of the dose. When the index approaches 20 the treatment is stopped for 24 to 48 hours mostly; it is then resumed with smaller doses.

The daily reading of the prothrombin index is not absolutely necessary and out-patient treatment with synparin may therefore be made possible.

### References.

- 1) Allen, E. V., Barker, N. W., and Waugh, J. M.: A Preparation from Spoiled Sweet Clover (3,3'-Methylene-Bis-(4-Hydroxycoumarin) Which Prolongs Coagulation and Prothrombin Time of the Blood. *J. Amer. Med. Ass.*, 120, 1009, 1942. — 2) Bingham, J. B., Meyer, O. O., and Pohle, F. J.: Studies on the Hemorrhagic Agent 3,3'-Methylene-Bis-(4-Hydroxycoumarin) I. *Amer. J. Med. Sci.*, 202, 563, 1941. — 3) Bingham, J. B., Meyer, O. O., and Howard, B.: Studies on the Hemorrhagic Agent 3,3'-Methylene-Bis-(4-Hydroxycoumarin). A Report on further Clinical Observations. *Amer. J. Med. Sci.*, 205, 587, 1943. — 4) Bruzelius, S.: Dicoumarin in Clinical Use. *Acta chir. scand.*, 92, 1945, suppl. C. — 5) Butt, H. R., Allen, E. V., and Bollman, J. L.: Preparation from Spoiled Sweet Clover, 3,3'-Methylene-Bis-(4-hydroxycoumarin), Which Prolongs Coagulation and Prothrombin Time of the Blood. *Proc. Mayo Clin.*, 16, 388, 1941. — 6) Jansen, K. F.: »Dikumarin». *Disp. E. Munksgaard, Kbhvn.* 1944. — 7) Lehmann, J.: Protrombinbestämning i kliniken. En ny modifikation av Quicks metod. *Nord. Med.*, 12, 3192, 1941. — 8) Lehmann, J.: Försök till kurativ och profylaktisk behandling av tromboser med ett per-os-preparat (3,3'-Methylen-di-(4-hydroxycoumarin)). *Svenska läkartidn.*, 39, 73, 1942. — 9) Lehmann, J.: Thrombosis treatment and Prevention with Methylene-Bis-(Hydroxycoumarin). *Lancet*, I., 611, 1943. — 10) Meyer, O. O., Bingham, J. B., and Axelrod, V. H.: Studies on the Hemorrhagic Agent, 3,3'-Methylene-Bis-(4-Hydroxycoumarin). II. The Method of Administration and Dosage. *Amer. J. Med. Sci.*, 204, 11, 1942.
-

From the Medical Clinic of the University of Lund, Sweden.

## Intercapillary Glomerulosclerosis.

(Kimmelstiel-Wilson's Disease).

By

NILS ALWALL, CURT EKELEND and LEO ORAS.

(Submitted for publication July 10, 1949.)

In 1936, Kimmelstiel and Wilson described a syndrome which now bears their name. In their opinion the clinical syndrome of albuminuria, oedema and high blood pressure corresponded to definite pathological changes in the form of intercapillary glomerulosclerosis. They regarded the disease as rare and found it mostly in diabetics. Since this first report, several authors have written about the disease, and most of them considered the microscopical renal changes. The clinical material, however, is comparatively small.

In this paper we wish to report details of 5 of our 9 cases and give a short survey of the literature. The possibility of the clinical diagnosis of intercapillary glomerulosclerosis (i. g.) and the practical importance of such a diagnosis will also be discussed.

In 1943, one of us (N. A.) demonstrated a patient at the meeting of the Swedish Medical Association. This was apparently the first case reported in the Scandinavian countries. It was diagnosed clinically and verified by autopsy.

The following 5 cases showed diffuse renal changes of intercapillary glomerulosclerosis.

Two of these cases were treated entirely at the Medical Clinic of Lund, 2 at the Medical Department of the hospital at Växjö (Director: Otto Östberg, M. D.), and one (case 3), was treated first in Lund and later at the hospital at Växjö.

*Case 1:*<sup>1</sup> A man of 64 suffered from diabetes since the age of 44 and was treated by diet. At the age of 51, the right leg was amputated below knee because of gangrene and at 60 he had a cataract in left eye, which was removed. At the age of 62 he had proteinuria and oedema. His legs became swollen on exertion. The amount of protein in the urine fell from 1.1 to 0.4 % during a stay in hospital, but proteinuria continued.

<sup>1</sup> Reported at the Meeting of the Swedish Medical Association in Stockholm November, 27th, 1943.

Recently he developed cardiac asthma, his legs were swollen in the evenings, and he was treated at the Medical Clinic until he died on October 24th, 1943.

The legs, thighs and scrotum were extremely oedematous. Blood pressure 180/100 mm Hg. The heart was moderately enlarged. There was a bilateral pleural effusion. Protein in the urine 0.9—0.5 %. Plasma protein 5.8 mg%, albumen 2.9 and globulin 2.9 mg%. Hemoglobin 73 %, RBC. 3.53 millions per cmm. Sedimentation rate 50 mm in 1 hour; specific gravity 1.018; non-protein-nitrogen blood 46—37 mg%. Urea clearance 17 %. His diabetes was slight and did not require treatment with insulin but only a moderate limitation of the diet. The highest blood sugar value was 350 mg%. Serum cholesterol 185 mg%. — Senile cataract and left optic atrophy, but no hemorrhages in either fundus.

During a stay of 10 weeks at the clinic the patient was treated with digitalis, and his condition improved and his weight was reduced by 13 kg. Finally his temperature began to rise, and the patient died suddenly.

*Autopsy:* Hyaline changes in almost all glomeruli. The various ages of the lesions could be estimated from the variable degree of sclerosis. In some areas there are deposits of lipid material near the changes of interglomerular glomerulosclerosis. Widespread changes of a similar type were observed in the arterioles, but sometimes there was actual arteriosclerosis. Similar changes were found in the spleen, pancreas and liver, but less marked in the myocardium. Amyloid was not found.

*Case 2:* A man of 75. At the age of 70 years he was treated at first at the Medical Clinic for high blood pressure and aortic regurgitation. He was known to have had a high blood pressure for some 25 years. On admission the blood pressure was 245/85—220/80 mm Hg. The urine did not contain protein or sugar.

At the age of 71 diabetes was first diagnosed, for which he was given up to 24 units per day of protamine-zinc insulin, but he was discharged on a diet but without insulin. The beginning of a cataract were noted but there were no changes in the fundi.

Four years later he was readmitted on October 29th, 1945 and treated until his death on November, 28th. He had lost more than 20 kg in weight, and for the last 2—3 months he had been troubled by thirst, tiredness and balanitis. During the last month he had had 20 units of protamine-zinc insulin per day.

There was slight oedema around the ankles. Blood pressure 210/75 mm Hg. The heart was considerably enlarged. The urine contained traces of protein and occasionally pus. Plasma protein 7.1 mg%. Sedimentation rate 25 mm in 1 hour. Hemoglobin 91 %, RBC. 4.2 millions per cmm. Addis' count on urine: 5,000 RBC, 4,750 WBC and 300 granular casts per 12 hrs; maximum specific gravity 1.024. Only small numbers of bacteria were found in the urine. Blood non-protein nitrogen 40 mg%; urea clearance 95 %.

At first the patient improved slightly and the balanitis healed. His diabetes required 40 + 40 units of protamine-zinc insulin. Highest blood sugar value was 500 mg%. Gradually, however, bilateral gangrene of the feet developed and the patient died.

*Autopsy:* Chronic fibrous endocarditis with small warty excrescences, widening of the aortic valve ring, myocardial hypertrophy, pulmonary oedema. Diabetes mellitus. Amyloid disease of the islands of Langerhans. Generalised arteriosclerosis, renal arteriosclerosis. Gangrene of both feet. Inter-capillary glomerulosclerosis.

*Case 3.* A man of 39. At the age of 33 developed increasing thirst, tiredness and swollen legs in the evenings. He was admitted to Växjö Hospital for diabetes mellitus and proteinuria. During his stay there proteinuria was not observed. He had 52 units of insulin per day at first and later 24 units per day. Proteinuria off and on during the following 3 years.

At the age of 36 developed bilateral cataract. Recently he had oedema of the legs and attended the Medical Clinic of Lund. Blood pressure 230/140 mm Hg; protein in the urine 0.02—0.5 %. Blood non-protein nitrogen 75 mg%. Indican +; xanthoprotein 35 units. Urea clearance 13 %. Concentration test: maximal 1.016. Microscopy normal. Sedimenta-

tion rate 50 mm in 1 hour. Hb. 75 %. RBC 3.2 millions per cmm. Moderate diabetes, well controlled by 20 units of protamine-zinc insulin per day and diet. Bilateral cataract, retinitis and hemorrhages. Highest blood sugar value: 400 mg%.

He died later in another hospital from uremia and acidosis.

*Autopsy:* Intercapillary glomerulosclerosis.

*Case 4:* A woman of 25 suffered from diabetes mellitus since the age of 16. Insulin 96 units per day. The urine did not contain protein.

At the age of 23 she was very ill with right-sided pyelonephritis for which nephrotomy was performed. The urine contained many leucocytes and bacteria. Blood pressure 200/130 mm Hg, protein in the urine varied around 0.5 %. Blood non-protein nitrogen up to 48 mg%. During a pregnancy she developed increasing proteinuria and retinal hemorrhages.

During the last year of her life she had considerable oedema of the face, legs and arms and suffered from shortness of breath and impairment of vision. Blood pressure 300/200 mm Hg. Blood non-protein nitrogen 86 mg%, protein in the urine: 1 %. Many white corpuscles and bacteria persisted in the urine in spite of repeated treatment with urinary antiseptics, she had marked oedema of the optic discs. The sedimentation rate rose from 50 to 114 mm in 1 hour. Hb. 66 %. Blood sugar reached 440 mg%. Insulin was gradually reduced and for a short time she continued without it. Her heart became considerably enlarged. She died of increasing uremia with the blood non-protein nitrogen rising to 146 mg% and proteinuria varying between 0.08—0.09 %.

*Autopsy:* Nephrosis, intercapillary glomerulosclerosis.

*Case 5:* A woman of 20 had had diabetic coma when 8 years old. During the following years she received 36—40 units of protamine-zinc insulin per day. She had various infections at times. Some occasions she was almost comatose. Her highest blood sugar was 580 mg%. At the age of 15—16 protein in the urine was sometimes up to 0.1 % and she had a low blood pressure, but microscopy of the urine showed no abnormalities.

At the age of 18 she had acute left-sided iridocyclitis, but the optic fundi were normal. From then onwards she had recurrent superficial abscesses in different areas and constant proteinuria with many white blood corpuscles and bacteria in the urine, but blood pressure and blood non-protein nitrogen remained normal.

Recently she lost weight and was admitted to the medical department of Växjö Hospital, where miliary tuberculosis was found in her lungs with a cavity. The dose of insulin was gradually reduced from 40 to 24 units of protamine-zinc insulin. Protein in the urine was 0.55 %, plasma protein 4.8 mg%. Blood pressure 140/90 mm Hg; blood non-protein nitrogen 21 mg%. Sedimentation rate 108 mm in 1 hour. Hb. 77 %. RBC. 3.9 millions per cmm. Urine: Addis' count: 148,800 leucocytes, and 5,500 red cells. Specific gravity 1.025. The temperature rose to 40.3° C, and she died.

*Autopsy:* Miliary tuberculosis. Tuberculous cavities in the lungs. Intercapillary glomerulosclerosis.

Four other patients with i. g. have since been observed, whose symptomatology was similar to the cases described here.

### Discussion.

The following comments on the series of cases published so far survey the literature on this subject, partly in tabular form. Our own cases have been compared to those of other authors. Since completing these tables, we have observed 4 more cases, confirmed like the other 5 cases by autopsy.



## 1. Clinical Symptoms and Signs.

Table I shows the frequency of i. g. given by various authors and its relationship to diabetes.

In Tables II to IV, however, only cases with detailed information are included.

Owing to the difficulty of diagnosing the disease clinically, the tables only include cases confirmed by autopsy. In the tables the highest values of any investigation is given when several examinations have been made.

*A. Age distribution.* All authors agree that most cases of i. g. occur above 40 years.

However, Anson (1938) saw a patient of 35 years; Spühler and Zollinger (1943) 3 patients under 40 years; Laipply et al. (1944) a girl of 16; Goodof (1945) 2 girls of 17 and 19 respectively; and Dolger (1947) saw 3 patients under 20 years.

In Table II 7 % are under 40 years, 80 % 41—70 and 13 % more than 70 years old.

*B. Sex distribution.* Most authors have noted a predominance of women.

However, Laipply et al. (1944) find no difference between the sexes.

Table II shows 64 % women and 36 % men.

*C. Diabetus mellitus.* All the authors agree that the most marked changes of i. g. are found in diabetics.

Newburger and Peters (1939) and Spühler and Zollinger (1943) pointed out that mild diabetes may be masked by a rise of the renal sugar threshold.

The last authors observed a patient without glycosuria and a blood sugar value of 500 mg%; they also pointed out that i. g. diagnosed at autopsy should lead one to suspect that diabetes had been present in life even if it has been missed. Herbut (1941) and Allen (1941) regarded i. g. as a criterion of diabetes.

The importance of blood-sugar examination and glucose tolerance tests in cases of suspect i. g. without glycosuria, must be stressed.

*a. Severity of diabetes.* All authors agree that slight diabetes is often complicated by i. g. Table III shows that 56 % of the patients had to use insulin and that 44 % were controlled by diet; the table indicates the doses of insulin needed in the various cases. Glycosuria has been reported in 75 %. The blood-sugar was 111—120 mg% in 24 % and more than 200 mg% in 76 % of cases.

Spühler and Zollinger (1943) reported 2 patients under 30 years, who required 70 and 80 units per day respectively. Laipply et al. (1944) reported a girl of 16 with severe diabetes but the dosage of insulin is not stated.

*b. Duration of diabetes.* As a rule diabetes has been present before the renal symptoms became manifest. Of all the cases in Table III only 1 showed renal symptoms before the onset of diabetes. In 13 % diabetes was known for about a year before the renal disease was diagnosed, in 32 % it had been present 1—5 years and in 53 % 6—20 years.

Lukens and Dohan (1946) produced diabetes in a dog by injecting pituitary extract. Diabetes persisted for 5 years after the injections. At autopsy slight but typical changes of i. g. were found.

*D. Hypertension.* Table III shows that the systolic blood pressure was to 149 mm Hg in 11 % of cases. 150—199 mm in 38 % and higher than 200 mm in 51 %. The diastolic pressure was above 100 in 63 %.

Kimmelstiel and Wilson (1936) found that hypertension was usually not malignant. Herbut (1941) and Siegal and Allen (1941) made similar observations. Spühler and Zollinger (1943) found »blasse Hypertonie».

According to Joslin (1937) the blood pressure increases more readily with increasing age in diabetics than in the corresponding age groups of normal subjects. Siegal and Allen (1941) and Laipply et al. (1944) believe that the blood pressure is higher in diabetics with i. g. than in diabetics of the corresponding age groups without i. g. Spühler and Zollinger (1943) suggest, that a normal blood pressure in cases of i. g. is due to cardiac failure.

*E. Oedema.* According to Kimmelstiel and Wilson (1936) the oedema has a nephrotic character. Other authors differ; oedema may be absent, but when it occurs with cardiac failure it shows the typical localization. Table III shows no oedema in 16 %, only in the lower extremities in 35 %, and generalised oedema in 49 %. The question of oedema and plasma proteins will be discussed below.

*F. Retinal changes.* Table III shows, that retinal changes occurs in 93 %, changes in the blood vessels of the retina in 20 %, and more severe changes with hemorrhages and exudates in 73 %.

Newburger and Peters (1939), Herbut (1941), Siegal and Allen (1941) and Spühler and Zollinger (1943) believe that in most cases of i. g. the retinal changes are more severe than in ordinary arteriosclerosis, and that they resemble those seen in chronic nephritis.

In this connection we will only mention the important publications of Ballantyne on micro-capillary aneurysms and phlebosclerosis.<sup>1</sup>

*G. The non-protein-nitrogen in the blood* was in 45 % of the cases between 41 and 100 mg%, and in 28 % more than 100 mg% (see Table IV).

Herbut (1941) reported such a high figure in one case of a series of ten and considered that it could not have been due to extra-renal causes. Spühler and Zollinger (1943) found in their patients who were less than 40 years that the non-protein nitrogen was normal, but that in older patients it was often high from the onset, especially when the patients were very ill. Before death it rose in all the cases, generally to more than 100 mg%. They stated that diabetic acidosis may contribute to the causation of uremia.

Newburger and Peters (1939) found that none of their patients with an increase in non-protein nitrogen lived more than a year.

*H. Proteinuria.* In the material presented in Table IV proteinuria occurs in 34 % at a level of up to 0.4 % and in 66 % it was more marked.

Spühler and Zollinger (1943) found pronounced proteinuria, often more than 1 %, in their younger patients with i. g., while the older ones only showed moderate proteinuria, usually about 0.1—0.4 %. Most authors such as Kimmelstiel and Wilson, Newburger and Peters, Siegal and Allen and others regard i. g. as a cause of proteinuria, while others point out, that cardiac failure and diabetic acidosis may play a part.

<sup>1</sup> Ballantyne, A. J.: *Modern Trends in Ophthalmology*, Ed. Sorsby, London, 1948. Friedenwald, J. S.: *Am. J. Ophthalm.* 1948: 32: 487.

*I. Specific gravity of urine.* Table IV indicates the highest figures for the specific gravity of the urine in the individual cases, but this must be regarded with caution for various reasons.

There is, for instance, no information whether the values have been corrected for glycosuria and proteinuria; therefore the values reported may have been too high. Some authors, e. g., Spühler and Zollinger (1943) mentioned that the value was obtained in some cases after the onset of thirst, but this does not seem to have been the case invariably.

The specific gravity of the urine was in 40 % of the cases more than 1.020 and in 60 % it was less than 1.020.

*J. Urinary sediment.* For the differential diagnosis of chronic nephritis, the examination of the urinary sediment is of great value, but information on this matter is as yet too scanty.

Newburger and Peters (1939) did not usually find red corpuscles in the urine, but in 1 case 1 red corpuscle per field was seen, Siegal and Allen (1941) found slight haematuria in 1 case with nephrotic syndrome. Spühler and Zollinger (1943) saw several cases with red cells in the urine. Hyaline and granular casts are found occasionally.

*K. Hemoglobin.* Values of less than 75 % were observed in 57 % of the cases. This information is insignificant without full investigation. Newburger and Peters also observed the usual combination of a rise of blood non-protein nitrogen and anemia in cases of i. g.

*L. Plasma protein.* Only few authors have estimated the plasma protein. The results (see Table IV) show that 6 % of the cases had a plasma of = 4 %, 40 % had a value of 4.1—5 %, 40 % had 5.1—6 % and 14 % had more than 6 %.

Spühler and Zollinger (1943) found low plasma protein values in young and middle aged patients, who had proteinuria and at the same time generalized oedema. Siegal and Allen (1941) found the same in cases with marked oedema. Newburger and Peters (1939) observed that the amount of plasma protein depended on the degree of proteinuria and the protein intake in the food.

*M. Serum cholesterol.* In 26 cases shown in Table IV 201—300 mg% was found in 31 % of cases, and more than 300 mg% in 58 % of cases; 11 % had values of less than 200 mg%.

Among 14 patients with the nephrotic syndrome and hypoproteinemia, Siegal and Allen (1941) found 12 with a serum cholesterol of more than 400 mg% and some had 600—700 mg% on occasions. In the series reported by Spühler and Zollinger (1943) patients with a marked nephrotic syndrome were found to have higher values of serum-cholesterol.

*N. Nephrotic syndrome.* This syndrome is found in 58 % of cases, but different authors give different definitions of the syndrome, as is apparent from the subsequent paragraphs.

Kimmelstiel and Wilson (1936) defined the nephrotic syndrome as follows: oedema of the renal type, spreading to arms and face, and marked proteinuria. Newburger and Peters (1939) added a third sign: low plasma protein; Siegal and Allen (1941) added a fourth: increased serum cholesterol.

The relationship of age to the formation of the nephrotic syndrome is discussed by Spühler and Zollinger (1943).

They found a fully developed nephrotic syndrome mostly in younger and middle aged patients with i. g. At first some of their patients had normal blood pressures and the renal function was not disturbed, *i. e.* normal non-protein nitrogen, good renal concentrations and good excretion.

Opinions on the nephrotic syndrome vary.

Newburger and Peters (1939) believed that the degree and duration of proteinuria and the protein intake in the food are of great importance in this connection. Their material, however, shows that this is not always the case and in spite of a diet rich in protein, one of their patients with i. g. developed hypoproteinemia with proteinuria.

Cardiac failure caused by hypertension may give rise to oedema and this may complicate matters.

## 2. Diagnosis.

The difficulty of diagnosing i. g. during life is clear from the preceding notes.

Diabetes seems to precede i. g. But it is more often found in elderly persons, though sometimes also in the young. Diabetes may require large amounts of insulin, but thus on forms which can only be proved by a glucose tolerance curve.

The patients usually have a high blood pressure, but this may not be apparent at first. In younger and middle aged patients, who generally present a marked nephrotic syndrome, differential diagnosis is concerned with chronic nephritis with nephrosis or other causes of nephrosis such as lipoid- and amyloid nephrosis. In older patients, who generally have only slight proteinuria and no oedema, or oedema which may be due to cardiac failure from hypertension differential diagnosis is concerned with hypertension.

A history of acute nephritis may support the diagnosis of chronic nephritis. If such information is absent, the diagnosis is almost impossible. Nephrosis may be found in either case; at first i. g. may be confused with nephrosis without hypertension. The course of both is characterized by a high blood pressure, often reduced renal function and red cells, casts and protein in the urine. The differential diagnosis is made more difficult because chronic nephritis with nephrosis may occur without hematuria. In doubtful cases with nephrosis and slight diabetes, i. g. should be considered as a possibility according to Auroi (1943) if the patient is over the age of 40 years.

In older patients, where a nephrotic syndrome is less common, the differential diagnosis may have to include i. g. or hypertension with nephrosclerosis or chronic nephritis. Spühler and Zollinger (1943) pointed out that proteinuria is generally more marked in i. g. than in nephrosclerosis. Intercapillary glomerulosclerosis and chronic nephritis may, of course, co-exist in one and the same patient.

Kimmelstiel and Wilson (1936) studied a patient with symptoms and signs which might have suggested i. g. or chronic nephritis with diabetes. At autopsy the typical changes of both were found. Spühler and Zollinger (1943) saw a patient of 38 with severe diabetes, high blood pressure, proteinuria, oedema and retinitis. Autopsy confirmed both i. g. and chronic nephritis.

It seems almost impossible to make a clinical diagnosis of i. g. with any certainty, when the differential diagnosis includes i. g. and chronic nephritis, and i. g. and hypertension with nephrosclerosis respectively.

Hilden (1945) suggested that it might be possible to obtain help in the differential diagnosis of i. g. from urea and diodrast clearance tests. Unfortunately his case was not confirmed by autopsy.

Amyloid disease of the kidneys should be suspected in cases of chronic suppuration, but it may occur without obvious chronic infection and it is also found in diabetics with hypertension. Amyloid disease of the kidneys sometimes does not become manifest until old age, and it may run a course with hypertension and retinitis.

Differential diagnosis on clinical grounds between i. g. and amyloid disease of the kidneys is very difficult and often impossible.

It is interesting to learn that Spühler and Zollinger (1943) believe that infection or another toxic condition always precedes i. g.

A positive Congo red test has been regarded as an indication of amyloid disease, but is, of course, not specific. The dye is also retained in lipoid nephrosis, though to a lesser degree. Fahr (1942) observed a patient in whom amyloid disease was diagnosed by the Congo red test but at autopsy no evidence of amyloid disease, but i. g. was found.

Lipoid nephrosis is rare and mainly found in the young and it runs a course without hypertension and without impaired renal function, but in i. g. the renal function may be normal at first.

Hilden (1945) stated, that diabetes, nephrosis and essential hypertension rarely co-exist.

*All authors agree that it is impossible to diagnose i. g. during life with accuracy.*

Goodof (1945) stated that the possible diagnosis of i. g. should be considered in cases of slight or moderate diabetes which has persisted for more than 6 years; if after that period a patient begins to excrete moderate or large quantities of protein without evidence of any other definite renal disease i. g. should be suspected.

### 3. Prognosis.

It is agreed that the prognosis in fully developed cases of i. g. is bad.

No patient with a raised non-protein nitrogen has survived for more than a year (Newburger and Peters; 1939). Of 11 cases 7 died within 2—3 years from the onset of the renal symptoms, uremia or cardiac failure (Siegal and Allen; 1941). All patients died within 2—4 years from the beginning of renal symptoms (Spühler and Zollinger; 1943).

Table II summarizes the cause of death reported in cases of i. g.: 33 % died of uremia, 31 % of cardiac failure, 11 % of pneumonia, 6 % of diabetic gangrene and 19 % from other causes.

The last group includes 3 cases of cerebral hemorrhage, 2 cases of miliary tuberculosis and 1 case died of peritonitis and ascending pyelitis following a prolonged stay in bed.

#### 4. Treatment.

No specific therapy in cases of i. g. has been found helpful, but hypertension or cardiac failure must be dealt with, nephrotic oedema may require a high protein diet and so on.

#### 5. Etiology.

The etiology is unknown, but various hypotheses have been put forward.

Kimmelstiel and Wilson (1936) thought that arteriosclerosis and diabetes are contributory causes of i. g.; Porter and Walker (1941) believed that it is a process of senescence accelerated by diabetes. Fahr (1942) and Spühler and Zollinger (1943) emphasized the importance of diabetes for the metabolism; the Swiss authors suspected infection as an etiological factor.

#### 6. Histo-Pathology.

A discussion of the pathology of the disease is outside the scope of this paper.

#### Summary.

With a survey of the literature we report 5 (9) cases of intercapillary glomerulosclerosis (Type Kimmelstiel and Wilson); in every case the diagnosis was confirmed by autopsy. The clinical picture in our cases was the same as in other published studies. Our cases have been added to the tabular representation of earlier results. Our cases also illustrate the difficulty and often impossibility of diagnosing i. g. during life.

We have not reported any of our cases where the diagnosis of i. g. was made clinically, but where autopsy showed chronic nephritis.

#### References.

- Allen, A. C.: Arch. Path. 1941: 32: 33. — Alwall, N.: Nord. Med. 1944: 24: 1849. — Anson, L. J.: South. Med. J. 1938: 31: 12 2. — Auroi, Marc: Schweiz. Med. Wschr. 1943: 73: 990. — Dolger, H.: J. Amer. med. Ass. 1947: 134: 1239. — Fahr, T.: Virchow's Arch. 1942: 309: 16. — Fishberg, A. M.: »Hypertension and Nephritis», Philadelphia, 1939, page 694. — Goodof, I. I.: Ann. Intern. Med. 1945: 22: 373. — Herbut, P. A.: Arch. Path. 1941: 31: 501. — Hilden, T.: Nord. Med. 1945: 27: 1749. — Horn, R. C., and Smetana, H.: Amer. J. Path. 1942: 18: 93. — Joslin, E. P.: »The treatment of Diabetes Mellitus», London, 1937. — Kimmelstiel, P., and Wilson, C.: Amer. J. Path. 1936: 12: 83. — Laipply, T. C., Eitzen, O., and Dutra F. R.: Arch. Intern. Med. 1944, 74: 354. — Lukens, F. D. W., and Dohan, F. C.: Arch. Path. 1946: 41: 19. — Newburger, R. A., and Peters, J. P.: Arch. Intern. Med. 1939: 64: 1252. — Porter, W. B., and Walner, H.: J. Amer. med. Ass. 1941: 116: 459. — Siegal, S., and Allen, A. C.: Amer. J. Med. Sci. 1941: 201: 516. — Spühler, O., and Zollinger, H. U.: Dtsch. Arch. Klin. Med. 1943: 190: 321; Schweiz. Med. Wschr. 1943: 73: 1430. — Volhard, E.: »Handb. inn. Med.» 1931, vol. 6.

Table I.  
*Interacapillary glomerulosclerosis (I. g.)*

Authors	Autopsies		I. g.		Clinical diagnoses of i. g.	Total number of cases of i. g. diagnosed clinically or by autopsy
	Total number	Diabetes found in life	Total number	Diabetes found in life		
Kimmelstiel and Wilson...	—	—	8	7	0	8
Anson .....	900	—	6	6	0	6
Newburger and Peters ....	174	—	5	4	5	10
Porter and Walker .....	—	—	6	6	2	8
Herbut .....	2,000	—	10	9	0	10
Siegal and Allen .....	305	105	36	35	7	43
Horn and Smetana .....	550	144	87	33	0	87
Fahr .....	—	—	30	23	0	30
Spühler and Zollinger ....	—	26	14	13	6	20
Auroi .....	—	—	2	2	2	4
Laipply, Eitzen and Dutra	332	124	84	79	0	84
Goodof .....	10,000	214	<sup>1)</sup>	94	0	—
Hilden .....	—	—	1	1	1	2
Present series .....	—	—	5	5	—	5

<sup>1</sup> 10—30 %.

Table II.  
*Cases of intercapillary glomerulosclerosis confirmed by autopsy.*

Authors	Total number	Age			Sex		Cause of death					
		up to 40	41—70	More than 70	Men	Women	Total number	Uremia	Cardiac failure	Pneumonia	Gangrene	Other causes
Kimmelstiel and Wilson .....	8	0	8	0	3	5	8	2	5	1	0	0
Newburger and Peters .....	4	0	4	0	1	3	4	0	0	1	1	0
Porter and Walker .....	6	0	6	0	4	2	6	0	2	2	—	2
Herbut .....	10	1	7	2	4	6	—	—	—	—	—	—
Siegal and Allen .....	14	0	14	0	4	10	14	5	6	2	1	0
Fahr .....	30	0	25	5	10	20	—	—	—	—	—	—
Spühler and Zollinger .....	14	3	7	4	5	9	13	6	2	0	0	5
Auroi .....	2	0	2	0	0	2	1	0	0	0	0	1
Hilden .....	1	0	1	0	0	1	1	0	0	0	0	1
Present series .....	5	3	1	1	3	2	5	2	1	0	1	1
Total number	94	7	75	12	34	60	52	17	16	6	3	10
Percentage	—	7	80	13	36	64	—	33	31	11	6	19

Table III.

Cases of intercapillary glomerulosclerosis confirmed by autopsy classified for symptoms and signs.

A u t h o r s	Duration of diabetes before renal symptoms in years				Treatment of diabetes				Blood sugar				Glycosuria				Blood pressure in mm Hg systolic				Oedema				Retinal changes					
	Number of cases	Less than a year	About 1 year	1-5	6-20	Number of cases	Diet only	Insulin $\leq 20$ I. U./day	Insulin $> 20$ I. U./day	Number of cases	$\leq 110$ mg%	111-200 mg%	$> 200$ mg%	Number of cases	No glycosuria	Glycosuria	Number of cases	$\leq 149$	150-199	$> 200$	Diastolic $> 100$	Number of cases	No oedema	Oedema in lower extremities only	Generalized oedema	Number of cases	No changes	Vascular changes	Hemorrhages, exudates	
Kimmelstiel and Wilson	6	0	0	3	3	—	—	—	—	1	0	0	1	5	1	4	7	4	1	4	4	7	0	2	5	1	0	0	1	
Newburger and Peters	4	0	1	1	2	3	—	—	—	4	0	3	1	4	2	2	4	4	0	2	4	4	4	0	1	3	4	0	0	4
Porter and Walker	6	0	3	3	0	5 <sup>1</sup>	—	—	—	6	0	0	6	6	2	4	6	1	3	5	2	6	10	1	8	4	5	0	3	2
Herbut	9	0	2	3	4	9	4	7	(5)	9	0	1	8	9	0	9	10	3	5	2	3	10	1	8	4	5	0	3	2	
Siegal and Allen	14	1	0	6	7	14	4	7	3	14	0	3	11	—	—	—	14	2	6	6	8	13	3	4	2	7	11	0	1	10
Spühler and Zollinger	13	0	1	2	10	12	5	5	2	—	—	—	—	—	—	—	14	0	4	10	12	13	4	2	7	11	0	1	10	
Auroi	2	0	0	0	2	2	1	1	0	2	0	2	0	2	2	0	2	0	0	2	2	2	0	0	2	2	2	0	1	1
Hilden	1	0	0	0	1	1	0	1	0	1	0	1	0	1	0	5	5	0	2	3	2	1	0	1	2	2	—	—	—	—
Present series	5	0	1	1	3	5	1	0	4	5	0	0	5	5	0	5	5	0	2	3	2	5	1	2	2	5	3	0	—	2
Total number	60	1	8	19	32	52	23	—	—	42	0	10	32	32	8	24	63	7	24	32	40	61	10	21	30	44	3	9	32	32
Percentage	—	2	13	32	53	—	44	—	—	—	0	24	76	—	25	75	—	11	38	51	63	—	16	35	49	—	7	20	73	73



Table IV.  
Cases of intercapillary glomerulosclerosis confirmed by autopsy which had been investigated clinically.

Authors	Blood non-protein nitrogen				Protein in the urine		Specific gravity of urine			Hemoglobin			Plasma protein				Serum cholesterol				Nephrotic syndrome		
	Number of cases				Number of cases		Number of cases			Number of cases			Number of cases				Number of cases				Number of cases		
	≤ 40 mg%	41-100 mg%	> 100 mg%		≤ 0.4 %	> 0.4 %	≤ 1.020	> 1.020		≤ 75 %	> 75 %		≤ 4 mg%	4.1-5 mg%	5.1-6 mg%	> 6 mg%	≤ 200 mg%	201-300 mg%	> 300 mg%		Not found	Present	
Kimmelstiel and Wilson .....	6	1	3	7	1	6	3	2	4	3	1	4	1	1	2	0	—	—	—	8	1	7	
Newburger and Peters .....	4	1	1	4	0	4	3	4	5	4	3	1	5	5	0	0	—	—	—	4	2	2	
Porter and Walker .....	6	1	0	6	1	5	4	1	5	4	4	1	0	0	0	0	—	—	—	6	2	4	
Herbut .....	9	1	3	10	8	2	3	3	10	1	2	—	—	—	7	0	—	—	—	14	7	7	
Siegal and Allen .....	14	7	3	13	3	11	5	8	13	9	5	11	4	3	3	3	0	1	2	13	6	2	
Spühler and Zollinger .....	13	2	5	14	6	7	10	2	14	1	1	10	1	0	1	1	0	1	1	2	0	0	
Auroi .....	2	0	0	2	1	1	2	0	2	1	1	2	0	0	1	1	0	0	1	3	1	2	
Hilden .....	1	1	0	1	0	1	1	0	1	3	2	—	—	1	1	1	1	—	—	5	3	0	
Present series .....	5	2	2	5	1	4	2	2	3	5	3	3	0	1	1	5	3	—	—	1	22	31	
Total number	60	16	17	62	21	41	33	22	44	19	25	35	2	14	14	5	26	3	8	15	53	22	31
Percentage	—	27	45	28	—	34	60	40	—	43	57	—	6	40	40	14	—	11	31	58	42	58	58

From the Medical Department of Rogaland Hospital, Stavanger, Norway.  
(Chief: Roald Opsahl, M. D.)

## Lupus Erythematosus Disseminatus.

### Report of two Cases.

By

GUNNAR VETNE.<sup>1</sup>

(Submitted for publication July 20, 1949.)

Since Libman and Sacks (1) in 1942 reported four cases of atypical endocarditis, two of which presented an eruption which closely resembled that of lupus erythematosus, many reports of a probably heterogeneous group of diseases which have been termed lupus erythematosus disseminatus or Libman-Sacks diseases, have appeared in the literature.

Arthralgia is an early and common symptom in this disease. Almost all the patients state that they have joint pains for several months or years before the actual onset of the eruption. All joints, particularly the smaller ones, may be affected. Deformities seldom develop, and only moderate changes are found in the roentgenograms.

Inflammation of the serous cavities commonly occurs. It usually takes the form of pleurisy but pericarditis and peritonitis are also seen.

Endocarditis, however, is not a constant feature. Reifenstein and Reifenstein (2) in 1939 reported 18 cases, 12 of which had endocarditis. When endocarditis is present it is usually of the type described by Libman and Sacks. It is characterized by the presence of warty proliferations on the cusps of several or all valves simultaneously. Further, isolated warty proliferations may be found on the cardiac wall. Aschoff nodes are present, and bacteria are not usually found.

Renal changes are often present. The clinical as well as the pathological picture resembles an atypical glomerulonephritis. The urine contains varying amounts of albumin, red blood cells and casts. The blood pressure is usually normal and the renal function is not impaired. The kidneys are usually normal in size or slightly enlarged. The microscopical picture varies. Bachr et al. (3) have demonstrated the presence of certain characteristic changes in the glomeruli consisting of a hyaline thickening of the basement membrane. They applied the term »wire loop lesion»

<sup>1</sup> Vei 1378, Annerud, Oslo, Norway.

to this change, which differs from the hyalinization seen in chronic nephritis. Later investigations, *e. g.* those by Stickney and Keith (4), have shown that these changes are found only in a comparatively small number of cases. In 15 patients with lupus erythematosus disseminatus they found renal changes in 7 and real «wire loop lesions» were encountered only in 3 cases. The changes in the other 4 cases resembled those of acute nephritis with proliferation of the vascular endothelium. Slight degenerative changes of the renal tubules were found in all cases.

Examination of a large control group comprising patients with various fatal diseases showed similar changes, *i. e.* slight degenerative changes of the glomeruli and renal tubules. They therefore think that the findings merely indicate the presence of a toxic nephritis which is not characteristic of lupus erythematosus disseminatus, and which may be caused by almost any serious disease.

The incidence of skin lesions varies according to various authors. Some authors maintain that a diagnosis of lupus erythematosus disseminatus cannot be made in absence of skin manifestations, while others have reported several cases without skin lesions. Skin manifestations were absent in 4 cases in Reifenstein's series. Apart from the «typical» eruption in the face, eruptions may also occur in other areas, particularly on the hands and feet. Areas exposed to light are predisposed, and the condition is aggravated by sunlight.

Some cases may show marked acrocyanosis of the hands and feet. Keratitis and iritis may also be seen.

Recent pathological investigations indicate that fibrinoid degeneration of the fibrous tissue of the skin, vessels, and internal organs is a common occurrence. The small vessels may show changes resembling those of a periarteritis nodosa.

Blood changes are usually present. There may be normochromic or hypochromic anaemia and changes in the albumin-globulin ratio with hyperglobulinemia. Eckerstrøm (5) has reported a case where the albumin-globulin ratio varied from 0.53 to 1.08. The plasma was examined by electrophoresis and the gamma globulins were found to be pathologically increased. The albumin-globulin ratio may vary within wide limits over a short period. In Eckerstrøm's case it rose from 0.66 to 1.08 in six weeks. Ten weeks later it fell to 0.53. In one of our cases the ratio fell from 2.17 to 0.49 in two weeks. This was due to an increase of the globulin fraction from 1.66 to 6.2 per cent while the albumin fraction remained unaltered.

The low leucocyte count is a remarkable feature in view of the fact that the disease runs a highly «infectious» course with pyrexia and an increased sedimentation rate. Leucopenia may be encountered, as in one of our cases. The differential count, however, reveals no significant changes.

The following 2 cases with the diagnosis of lupus erythematosus disseminatus were observed at Rogaland Hospital.

*Case 1.* Reg.nr. 3716/43. (This case has previously been shown by H. Øygarden to the Trondheim Medical Association.) A woman of 24 years with a healthy family history had no illness until January 1943 when the joints of the fingers became painful. Later on pain involved other joints. The pain moved from one joint to another, and in March 1943 it became so intense that the patient had to stay in bed. The temperature rose and a high remittent fever persisted. Three weeks before her admission on April 19th,

1943, a symmetrical eruption appeared in the face — on the nose and both cheeks — and on the medial aspect of both legs. On examination the patient appeared somewhat dull. On the nose and below both eyes an intensely red erythema, symmetrically distributed and sharply defined, was seen. The skin of the fingertips was bluish-red and desquamated. On the medial aspect of both legs were petechial hemorrhages. The temperature was  $38.4^{\circ}\text{C}$ , the blood pressure 125/75 mm Hg. The tongue was dry and greyish but greyish-black towards the base. (The patient said the tongue had become dark during the disease.) Otherwise the physical examination revealed nothing abnormal.

Nicotinic acid was given and a marked improvement of the exanthema in the face followed. The tongue became lighter in colour. The dullness improved also and the patient became more interested in her surroundings. The temperature, however, remained high and 10 days after admission it suddenly rose to  $41^{\circ}\text{C}$ . Sulfathiazole (total ogs 14 g) was given for 3 days, but she did not improve. There were no physical signs over the lungs. The white cell count, which was normal on admission, had now fallen to 2,900 per cmm with 41 per cent of granulocytes. For this reason a blood transfusion was given, and the condition apparently improved and the temperature fell to  $37.2^{\circ}\text{C}$ . During the next few days, however, it gradually rose to  $38\text{--}39^{\circ}\text{C}$ . The patient became increasingly listless. The hemoglobin fell from 62 (on admission) to 30 per cent in spite of repeated blood transfusions and injections of liver extract. The leucocyte count then rose to 11,200 but fell before her death on June 11th, 1943 to 6,800. She was delirious during her last few days.

Investigations: *Urine*: Heller's test was positive only intermittently. The benzidine test was negative. Microscopical examination showed some granular casts and some white but no red cells. *Blood*: The colour index was about 1 and remained fairly constant during her stay in hospital. The sedimentation rate was 104 mm on admission, but later on rose to 165 mm. (The readings were the same at room temperature and at  $37^{\circ}\text{C}$ .) *Plasma proteins*: May 13th: Albumin 3.59 per cent, globulin, 1.66 per cent, ratio 2.17. May 28th: Alb. 3.06 per cent, glob. 6.23 per cent, ratio 0.49. Bleeding and coagulation times normal. Platelet counts normal. Blood urea 54 mg per 100 ml. Sternal marrow biopsy revealed nothing abnormal apart from a slight preponderance of lymphoid cells. EKG: T-wave smaller in leads 1 to 3, high take-off of S-T<sub>4</sub>, negative T<sub>2</sub> (indicating myocardial damage). Radiographs of the chest were normal. Examination of the eyes (May 5th) showed retinitis with numerous superficial white spots and some radiating and patchy hemorrhages in both eyes.

The autopsy revealed the following findings: The pericardial cavity contained 200 g of clear yellowish fluid. There was no fibrin in the pericardium. The myocardium, endocardium, and valves were normal. The spleen was enlarged, and microscopical examination showed comparatively few follicles, some plasma cell and macrophage infiltration, and some large multinucleated reticulum cells. The kidneys normal in size and the capsules stripped off easily. The cut surface showed normal markings. Microscopical examination revealed slight degenerative changes in the renal tubules.

(The histological examination were carried out at the Pathological Laboratory of the Norwegian Radium Hospital.)

*Case 2.* Reg.nr. 1270/48. Woman of 48 years. Father died of tuberculosis. Two sisters mentally ill. The patient was healthy until september 1947 she started to have pains in the right thumb and forearm. In April 1948 stiffness and pain developed in the joints of the fingers, elbows, knees and ankles. She suffered from nausea and loss of appetite during the last two months before admission. She was admitted to hospital on August 17th, 1948, with the probable diagnosis of Rheumatoid Arthrititis. On admission she appeared depressed and tired. Tp.  $37.2^{\circ}\text{C}$ , blood pressure 100/50 mm Hg. Slight swelling of the left wrist with slight limitation of movements due to an old fracture. Otherwise nothing abnormal was noted on physical examination.

The patient had a remittent pyrexia up to  $40^{\circ}\text{C}$ . For a while she complained of abdom-

inal pain and nasty taste in the mouth. About 1 month after admission a symmetrical rash developed on the nose and on both cheeks. The administration of penicillin during the preceding week did not prevent the development of the exanthema. The rash gradually became deep red and more widespread on both cheeks and at the same time spread to the forehead and downwards to the neck where it was poorly defined against the healthy skin. The affected skin areas felt firmly like oedematous or infiltrated tissue. The patient was given nicotinic acid for six days (total of 1.2 g) after the appearance of the exanthema, which then gradually faded and had almost disappeared 2 days before her death.

On September 29th, she complained of pain in the chest. Harsh breath sounds and crepitations were heard over the base of the lung. A radiograph of the chest (Oct. 4th) showed a bilateral pleural effusion.

The patient's mental condition varied during her stay in hospital. Sometimes she was alert and cheerful, but more often she was depressed and apathetic and during the last few weeks before her death she was delirious. She became more and more cachectic and died on October 3rd, 1948.

*Investigations:* The blood pressure remained low during the entire in-patient period, and varied from 100/50 to 110/80 mm Hg. The Congo red test was negative following an Ewald's test meal. The ECG was normal. *Urine:* Heller's test was positive, the benzdine test negative. Microscopical examination showed some granular casts, a few red and numerous white blood cells. The albumin content rose from 0.1 to 0.7 per cent (Esbach's test) during the stay in hospital. *Blood:* The hemoglobin (77 per cent on admission) fell gradually despite 3 blood transfusions and iron and hydrochloric acid by mouth. On October 26th, the hemoglobin was 37 per cent and the colour index 1. The white cell count which was 15,500 per cmm on admission fell and was 2,600 on September 10th, but rose to 5,600 just before death. Sternal puncture was rather difficult. The smear revealed a poorly cellular marrow. The blood urea was increased during the initial period but later it returned to normal values. The platelet count was normal. Plasma proteins were 5.1 per cent on September 24th, and 5.2 per cent on October 2nd. The albumin-globulin ratio was not determined. Chlorides were 390 mg per 100 ml, and the blood calcium 8.9 mg per 100 ml. The sedimentation rate varied from 32 to 54 mm. Roentgenograms of the hands showed some decalcification, small defects and cystic areas near joints, and slight spur formations near the articular surfaces. Roentgenograms of the knees showed slight spur formations at the edges of the condyles. Pyelography was normal and so were the ocular fundi. A blood culture was negative.

The autopsy (14 hours post mortem) revealed the following findings: Dense pleural adhesions on the left side, slight adhesions on the right side. *Heart:* Some clear fluid was present in the pericardial sac, the pericardium was smooth and glistening. The size of the heart and the myocardium, endocardium and valvular cusps were normal. A microscopical section from the left ventricle showed ulceration of the endocardium and infiltration with leucocytes, macrophages and plasma cells. The inflammatory exudate extended into the myocardium. In the clot formed on the endocardium and in the vessels large numbers of bacteria, gram-positive cocci, were seen. *Kidneys:* The gross appearance and the cut surface were normal. Microscopical sections showed considerable inflammatory changes with necrosis of some glomeruli. Other glomeruli showed considerable proliferation of the cells of Bowman's capsule, and lymphatic infiltration. In some areas abscesses containing polymorph lymphocytes and plasma cells had formed around individual glomeruli. In some glomeruli the capillary loops were filled with gram-positive cocci but otherwise showed no evidence of inflammation. The renal tubules showed marked postmortem degeneration. Mallory's stain showed no particular thickening of the glomerular basement membrane. *Aorta:* The adventitia and the surrounding fibrous tissue showed considerable infiltration with plasma cells and lymphocytes. There was some fibrinoid degeneration and slight lymphocytic infiltration of the vasa vasorum.

*Spleen:* Weight 120 g. The cut surface had a normal colour but definite markings were absent. Microscopical examination revealed considerable congestion and large masses of gram-positive cocci within the vessels but no inflammatory reaction. The lymphoid structures were indistinct. *Adrenals:* The vessels were filled with gram-positive cocci. (The histological examinations were carried out at Dr. F. G. Gade's Pathological Laboratory in Bergen.)

### Comments.

Both these cases present most of the common signs of lupus erythematosus disseminatus, viz., joint phenomena, skin manifestations, blood changes, remittent fever and slight renal changes. No gross evidence of endocarditis was present. In case 2, sections showed infiltration with leucocytes, macrophages and plasma cells, but no vegetations were found on the valves and cardiac walls, as described by Libman and Sacks. It may be that the changes in our case represent an early stage of endocarditis. Ginzler and Fox (6), in 1941, described a case of lupus erythematosus disseminatus without macroscopical changes though histological sections revealed inflammatory changes of the mitral and tricuspid valves, and mural lesions, namely early endothelial proliferation and subendothelial infiltration with lymphocytes and fibroblasts. There is also the possibility that penicillin treatment may alter the appearances of the endocardial manifestations or even prevent their development.

The presence of bacteria in the heart and other organs may be due to invasion before or after death. The small abscesses surrounding some of the glomeruli contained bacteria which must be assumed to have been present before death. On the other hand, reactive changes were so slight that they could hardly have been of long standing.

The »septic» picture and the low leucocyte count so frequently found in lupus erythematosus disseminatus may be assumed to indicate a bacterial invasion of the organism during the later stages of the disease. It seems, however, that this invasion only affects the lungs. Of the 15 cases reported by Stickney and Keith, 7 had bronchopneumonia and one lobar pneumonia. According to the literature the other organs are seldom invaded by bacteria. A careful examination, however, may sometimes reveal the presence of bacteria in various organs. Adamson (7) reports 6 cases of lupus erythematosus disseminatus with bacteriological and serological findings covering the entire course of the disease, and a careful bacteriological examination at autopsy. In some of the cases hemolytic streptococci were found in the lymph nodes, tonsils and spleen. In other cases staphylococci, coliform bacilli or mixed bacterial flora were present. High titres of antistreptolysins and antistaphylolysins were found in some cases, but no definite relationship between the bacteria present and the titres was revealed.

None of our cases showed typical renal changes. In case 1 insignificant changes were encountered, and case 2 presented only slight changes of the glomeruli such as are seen in acute nephritis, and no »wire loop lesion».

The second patient for some time complained of intense abdominal pain and nasty taste in the mouth, and vomited on several occasions. This aroused the

suspicion of acute porphyria. The urine, however, was not dark-coloured, and urine-analysis revealed no evidence of porphyrinuria.

Reifenstein and several other authors have reported cases with longstanding and intense abdominal pain, but organic changes have not been demonstrated which may explain the abdominal pain.

Both our patients had a symmetrical rash in the face. It is noticeable that the exanthema and also the apathy in both cases improved following the administration of nicotinic acid. Whether the exanthema in lupus erythematosus disseminatus is due to lack of nicotinic acid is not clear from the literature and has not been fully investigated, though the improvement in our cases suggests it. Spontaneous regression of the exanthema can occur and some authors claim improvement following penicillin therapy. In one of our cases (case 2) the exanthema developed in spite of the administration of penicillin for a long time before its onset. Our patients did not suffer from diarrhoea which is a characteristic symptom in pellagra. The dark tongue which was seen in one case can scarcely be interpreted as a sign of pellagra, as »black tongue», to the author's knowledge, has never been observed in man.

Many cases of lupus erythematosus disseminatus which have been reported in the literature have presented with cerebral symptoms during the late stages of the disease, viz., convulsions, unconsciousness, stupor, hallucinations, etc.

Cai Holten (8) has reported a case where an epileptic seizure with tonic and clonic convulsions, dilatation of the pupils, and incontinence of urine and faeces occurred 3 days before death.

Both our patients had cerebral symptoms, period of apathy and melancholy alternating with restlessness and hallucinations, and finally, coma. The cause of cerebral symptoms is not known, and they do not occur frequently. Examinations of the central nervous system and the brain has not been carried out in many cases of lupus erythematosus disseminatus described. Stickney and Keith have reported one case with infarction of the brain. Multiple infarctions and emboli were demonstrated in this case. Reifenstein has reported one case who had clouding consciousness and incoherence for several weeks before death. In this case autopsy revealed a »slight adhesive meningitis».

The brain was not examined in our cases. As already mentioned, fibrinoid degeneration and changes resembling those of periarteritis nodosa have been found in blood vessels of several organs. These changes may possibly be present in the cerebral vessels also and thus cause circulatory disturbance which may give rise to the cerebral phenomena occurring in lupus erythematosus disseminatus.

### Summary.

The author report 2 cases of lupus erythematosus disseminatus. Endocarditis of Libman-Sacks' type was not present in either of the cases. In one case microscopical examinations showed ulceration of the endocardium and infiltration with

leucocytes, macrophages and plasma cells. This may possibly be interpreted as an early stage of the typical endocarditis.

In one case Gram-positive cocci were found in several organs, probably as a result of invasion just before death. This patient had leucopenia and granulocytopenia.

In both patients the exanthema was localized in the face, and in both it improved following the administration of nicotinic acid. In one of the patients the exanthema developed in spite of intensive penicillin treatment shortly before its onset.

In both cases various cerebral symptoms occurred. It is emphasized that these symptoms may be due to circulatory disturbance in the brain as a result of periarteritic changes of the small vessels.

#### Literature.

1. Libman, E., and Sacks, B.: Arch. int. med. 1924: 33: 701. — 2. Reifenstein, E. C., and Reifenstein, G. H.: Arch. int. med. 1939: 63: 553. — 3. Baehr, G.: Cit. according to Stickney and Keith. — 4. Stickney, J., Minott and Keith, N. M.: Arch. int. med. 1940: 66: 643. — 5. Eckerstrom, S.: Acta Med. Scand. 1948: 132: 21. — 6. Ginzler, A. M. and Fox, T. T.: Arch. int. med. 1940: 65: 26. — 7. Adamson, C. A.: Nordisk Medisin 1947: 33: 515.
-



From the University Clinic, Oslo. (Med. Dept. B. Director: Professor  
H. A. Salvesen M. D.).

## Periarteritis Nodosa — Asthma Bronchiale — Iododerma Tuberosum.

By

CARSTEN MÜLLER.<sup>1</sup>

(Submitted for publication July 25, 1949.)

Periarteritis nodosa (p. n.) is not a common disease. Since it was first described by Kussmaul and Maier in 1866 some 500 cases have been reported in the literature. In Norway the disease has been discussed by Harbitz (1917, 1921, 1926 and 1942), Opsahl (1938), Blegen (1941) and Homb (1946). In the majority of the cases reported the diagnosis was first made at autopsy. Blegen's case was recognized in life. Although p. n. is not common, it probably occurs more frequently than would appear from the literature.

The earlier conception of the specific infectious etiology of p. n. (bacteria, spirochaetes, vira) in recent years have given place to the theory of its allergic origin, which was first suggested by Gruber (1925) and has since been supported by clinical and experimental studies.

Cohen, Kline and Young (1936) considered that the arterial lesions are irreversible allergic reactions, and they emphasized the close resemblance of the changes to those found in experimental allergy (the Arthus phenomenon). The frequent connection of p. n. with rheumatic fever has been noted by Middleton and McCarter (1935). In support of the allergic theory it is further stated that p. n. is often accompanied by eosinophilia in the blood, but this is by no means a constant phenomenon. Thus Harris, Lynch and O'Hare (1939) found eosinophilia in only 19 of 101 cases of p. n., and Rackemann and Greene (1939) in 22 of 229, that is to say in little more than 10—20 per cent. In favour of the view that the disease is of allergic nature are also a number of experimental studies, in which, on sensitization with various substances (Metz: foreign proteins, streptococci, — Rich and Gregory: foreign proteins, sulphathiazole, — Friedberger and Ito, and Jacobs: iodine, — Selye: desoxycorticosterone), it was found possible to induce tissue-changes identical with p. n. in animals (rabbits, rats, guinea-pigs). Typical changes

<sup>1</sup> Majorstuveien 25 D, Oslo, Norway.

have been found in patients who died after serum sickness (Clark and Kaplan, Rich).

The *morbid anatomy* of p. n. is characterized by inflammatory changes in the walls of the small and medium-sized arteries, either of segmental or total distribution, and with local or general diffusion. Fibrinoid necrosis in the media is the primary lesion and there are also swelling of the wall, destruction of the elastic coat and infiltration with granulocytes, many of which are eosinophiles, and with mononuclear histiocytes. According to Arkin (1930) four stages can be distinguished: 1) a degenerative, 2) an acute inflammatory, 3) a granulation-tissue stage and 4) a healing stage. Quite often all the stages are found simultaneously, sometimes even in the same artery. From the media the process spreads, partly inwards towards the intima, causing local thrombosis and perhaps obliteration and infarction, and partly to the adventitia, with the result that small aneurysms develop, which may rupture and cause hemorrhage. The net result is a *necrotic panarteritis*. The periarteritis is neither primary nor constant, and Dickson (1907) has therefore suggested the name *polyarteritis nodosa*, emphasizing the presence of multiple foci. The characteristic periarterial nodules are, however, found in little more than 10 per cent of the cases. The most adequate designation of the disease would therefore be *allergic polyarteritis*.

All the organs of the body may be attacked, but most frequently the kidneys, heart, liver, gastro-intestinal tract, muscles, spleen, lungs, peripheral arteries and the central nervous system. They may be attacked separately, but more often in various combinations. The clinical picture of p. n. is very pleomorphic, and it is not intended to discuss the symptomatology with its variations. One particular set of symptoms must, however, be specially mentioned. P. n. is not infrequently present in cases of *bronchial asthma*, where *transitory pulmonary infiltrations*, *leucocytosis with extreme eosinophilia* and *phenomena suggestive of polyneuritis* are not uncommon findings. Rackemann and Greene (1939) have stated that asthma, numbness of the legs and eosinophilia of more than 25 per cent are indicative of p. n., and they point out that such cases frequently show hypersensitivity to drugs, especially to sulphonamides and iodine. The combination of bronchial asthma and p. n. has also been reported by Bergstrand (1939) (4 cases), Cohen, Kline and Young (1936) (3 cases) and Curtis and Coffee (1934) (3 cases). Tisell (1939) has described a case of asthma, eosinophilia (49 per cent), polyneuritis, oedema, severe abdominal pain, purpura, pulmonary infiltrations, pleural exudate and ascites, ending in death from ileus. P. n. was diagnosed at autopsy. Svanberg (1944) has recorded the case of a woman with asthma, sinusitis, infiltrations in the lungs, polyneuritis, leucocytosis (up to 45,000) and severe eosinophilia (75 per cent), where the diagnosis of p. n. was made post mortem. Such leucocytosis with considerable eosinophilia has been termed *Eosinophilia leucaemoides* by Engbæk, Heerup, and Thomsen (1942), who regarded it as an allergic reaction to various injurious agents. The importance of drug hypersensitivity is shown by a case published by Olesen (1948): A 20-year-old man with asthma and sinusitis developed fever during treatment with alphasol and was then given sulphathiazole. A rash followed and also proteinuria, pains in the extremities, abdominal pain, attacks of

vomiting and blood in the stools, as well as leucocytosis and eosinophilia (59 per cent). This patient was diagnosed in life as most probably p. n., and this diagnosis was confirmed by autopsy. Harkavy has described similar cases.

### Case Reports.

In the Department B of Medicine of the University Clinic, Oslo, a case of this type has been observed. In this case p. n. was diagnosed by means of biopsy. As there was apparently hypersensitivity to iodine, following the protracted use of potassium iodide, treatment with this drug was discontinued. Clinical improvement followed with partial regression of the symptoms, and the patient is still alive after nine months.

*Case 1.* J. S., a woman of 28 years. Apart from typhoid fever in 1939, she had previously been healthy. In the last 2 or 3 years she has had *bronchial asthma*. In January 1948 she began to get an eruption on the face, after taking potassium iodide for about 6 months. On February 26, 1948 she was admitted to the Dermatological Department of the University Clinic, where *iododerma tuberosum* was diagnosed. The efflorescences were mostly localised on the face — in the form of wartlike or fungoid prominences, especially on the nose, forehead and cheeks. Potassium iodide was stopped, and the skin affection gradually subsided. She was then transferred to the Department B of Medicine for treatment of her asthma.

During the first part of her stay in hospital she was considerably distressed, almost in status asthmaticus. She had temperatures and was treated with penicillin inhalations and autogenous vaccine. She complained periodically of *colicky abdominal pain* and occasionally had loose, mucous stools with a little blood. The radiographs showed *transitory pulmonary infiltrations* on both sides. The sputum grew various pathogenic microbes, but no tubercle bacteria. Pirquet's test was negative. The heart was normal. Electrocardiogram normal, blood pressure 110/70 mm Hg. She complained of paresthesia in hands and feet, and had pareses with symmetrical muscular atrophy, loss of sensitivity, tenderness on deep pressure and weakened tendon reflexes, and a diagnosis of *polyneuritis* was made.

The urine contained 0.05—0.1 per cent of protein, but the kidney function was good. (Blood urea 18 mg per cent, ura clearance 82 per cent.) Otherwise, there were no abnormal constituents in the urine.

*Blood examination* revealed no anemia, but considerable *leucocytosis*, rising to 38,000, and marked eosinophilia, which rose from 27 to 73 per cent. Platelets: 595,000 per cmm. Sedimentation rate 34, 49 and 28 mm in 1 hour. Serum proteins 6.75 per cent, albumin 3.48, globulin 3.27 per cent. Wassermann's reaction negative.

*Sternal puncture:* 60 to 70 per cent of the nucleated cells were eosinophilic granulocytes, most of them mature cells with 2 or 3 segments, while some were of stab cell, metamyelocyte or myelocyte type. The picture did not suggest leukemia.

*Muscle biopsy from pectoralis major* (Fig. 1): The muscle showed well-preserved striation and structure. In the centre of the largest portion was a small artery of muscular type, of which the wall was completely altered. In the lumen were threads of fibrin and some scattered leucocytes. The intima and media showed none of the usual regular layers, but consisted of an inner ring of fibrin with increasing leucocytic infiltration towards the periphery. The leucocytes in this part were mainly neutrophil granulocytes, and there were numerous nuclear droplets. The outer contour of the vessel was marked by a layer of deeper red colour. Around the vessel was a cellular band of histiocytic cells, neutrophil

and eosinophil granulocytes, lymphocytes and a few plasma cells. This cellular infiltration ended rather abruptly, and followed the contour of the vessel. There were no giant cells, but a few binucleated cells. *Diagnosis: Acute allergic arteritis* (L. Kreyberg).

*Subsequent course:* When the iododerma disappeared the patient gradually improved both as regards her asthma and the other symptoms. The number of leucocytes fell to 14,800, but there was still pronounced eosinophilia (61 per cent). The improvement in the polyneuritic was most marked, and the pulmonary infiltration disappeared. On June 15, 1948 she was discharged improved.

*Six weeks later* (July 27, 1948) she was readmitted in status asthmaticus, which was relieved by ordinary treatment. After this attack she appeared to be better than before. The polyneuritis had improved further, the lungs were normal on radiographic examination and the eosinophilia had fallen to 16 per cent of 16,000 leucocytes. The urine still contained a little protein, but the renal function remained good. Unfortunately, she would not agree to another muscle biopsy. On August 6, 1948 she was discharged in good health, free from asthma, with the instruction to avoid iodine in any form in the future.

A woman of 28 years suffering from bronchial asthma, developed iododerma tuberosum after 6 months' treatment with potassium iodide. Her general condition gradually deteriorated. There were low pyrexia, loss of weight, recurrent pulmonary infiltrations of non-specific nature, proteinuria without impaired renal function, abdominal colicky pain

with diarrhea and signs of polyneuritis. Leucocytosis with severe eosinophilia up to 73 per cent was noted. Muscle biopsy confirmed the provisional diagnosis of periarteritis nodosa.

After potassium iodide was stopped, all symptoms, except the asthma gradually improved. Two months after the biopsy she was well, and the eosinophilia had fallen to 16 per cent of 16,000 leucocytes.

In view of Rackemann and Greene's statement that asthma with eosinophilia of more than 25 per cent, and polyneuritic phenomena should be regarded as indicative of p. n., our records of cases of bronchial asthma were surveyed with a view to find analogous cases. It appeared that there had been another patient with



Fig. 1.

equally marked eosinophilia. It was interesting that this patient presented a picture very similar to that which has been described.

*Case 2. I. R.*, a woman of 34 years. Since 1942 she had suffered from *asthmatic bronchitis*. Later she had bouts of coughing mostly in the summer, with dyspnea and expectoration. She was treated with vaccines, asthma cigarettes and «cough mixtures», but there is no record as to whether she was taking potassium iodide from the beginning.

From January 1943 onwards she had pains in various parts of the body, had periods of fever and steadily lost weight.



Fig. 2.

While in hospital (Med. Dept. B, from February 27, 1943) she was constantly feverish, had a cough, but no tubercle bacteria were seen in the sputum. She had bronchitic sounds over the lungs and rhinitis with a watery secretion, which was regarded as *allergic rhinitis*. Blood pressure 105/80 mm Hg. Urine normal. No anemia, but *leucocytosis* (16,000 white cells) and *eosinophilia* (45 per cent). Sedimentation rate 83 mm/1 hour. Radiographs of the chest showed *bilateral pulmonary infiltrations*. During her stay in hospital, the temperature fell, the pulmonary infiltrations subsided and disappeared after 7 weeks, and at the same time the *leucocytosis* and *eosinophilia* decreased.

In the beginning of June 1944, she developed symptoms of pneumonia in the right lung, which disappeared without treatment, but in the following attack she began to feel more debilitated, lost appetite, again had fever and was periodically troubled by asthma. Two weeks after this pneumonia she developed a general outbreak of *purpura*, and got transitory *articular pains* and *diarrhea*.

She was admitted to Drammen Hospital on July 8, 1944, and was ill and thin, but only slightly troubled by her asthma. There was diffuse *purpura*, moderate anemia (Hb. 82 per cent, RBC. 3,770,000 per cmm), *leucocytosis* (26,500), severe *eosinophilia* (64 per cent). Platelets 380,000. Normal bleeding and coagulation times. With Hess' test a few petechiae were seen. Sedimentation rate: 118 mm/1 hour. Urinalysis showed *proteinuria* (about 0.25 per cent). In the blood moderate *azotemia* (urea 88 mg per 100 ml) was found, later falling to normal levels.

Radiographs of the chest: *Bilateral pulmonary infiltrations* which were not affected by chemotherapy. Examination of the heart revealed nothing abnormal. Electrocardiogram showed right ventricular preponderance and low voltage curves. She had oedema in the face.

*Subsequent course:* The patient developed anemia, her hemoglobin fell to 60 per cent. The *leucocytosis* persisted (27,000) and the *eosinophilia* rose to 69 per cent. In the *sternal marrow* was marked *eosinophilia*. Several blood transfusions were given, and the hemoglobin temporarily reached 100 per cent. The *purpura* gradually disappeared. Because of





the vascular factor is not prominent, but in the severe cases it manifests itself in forms varying from the benign transitory pulmonary infiltrations with eosinophilia, to the fully developed picture of periarteritis nodosa, with more stationary infiltrations and irreversible lesions of the vessels.

*Polyneuritis* when accompanied by p. n. is usually regarded as a result of obliterative lesions in the nutrient arteries of the peripheral nerves.

It is remarkable that in Case 2, which had *renal symptoms* and came to autopsy, the renal arterioles showed sclerosis and fibrosis without cellular reaction, but with thrombus formation and recanalization in several places, which were interpreted as endarteritis. The question arises whether we are dealing here with an inflammatory process which has run its course (where the cellular reaction has given way to fibrosis and sclerosis), or with a primary arteriolosclerosis. The latter possibility seems to have little foundation in a case of 34 years' age without hypertension. Even though we did not find any active periarteritis nodosa, yet the changes observed are compatible with the sequelae of p. n. (Arkin's stage 4).

In this connection an observation made by Keegan (1925) is of interest. A patient was thought to have a surgical condition in the right kidney, which was therefore removed. Histological examination revealed p. n. corresponding to Arkin's stage 2. The patient died 3 months later, and autopsy revealed fibrosis in the arterioles of the remaining kidney with thickening of the intima, and organized and canalized thrombi, analogous to the cicatricial stage of p. n. It is therefore probable that in our Case 2 there had been active p. n. several months before death. This cannot be proved as biopsy was not performed, but in view of the close resemblance to the changes described in Case 1, where p. n. was demonstrated in life, a connection between the vascular lesions seen and the hypersensitivity seems to provide the most plausible explanation of the condition.

The relationship between *drug hypersensitivity* and allergic diseases of the vessels (Periarteritis nodosa) has been illustrated by experiments and by clinical experience. Landsteiner (1936) showed that certain chemicals can combine with homologous proteins in the serum and can modify these proteins so that they acquire antigenic potency. The organism is sensitized to this complex and therefore to the drug. It is difficult to explain why only few individuals have this tendency.

Asthmatics show this tendency to drug hypersensitivity to a greater extent than others. In such individuals drug allergy often comes in addition to the already existing hypersensitivity which causes the asthma, and this combination in some cases may lead eventually to irreversible vascular lesions, analogous to Harkavy's «vascular allergy». The risk of such a development is particularly present where the administration of the allergen producing drug is continued in spite of symptoms which warn of impending danger, such as drug fever, rash, purpura, eosinophilia. There is reason to suppose that Astwood is correct when he regards «drug fever» and serum sickness as mild, reversible manifestations of allergic arteritis and when he states that all transitions from these maladies to the severe, generalised cases of p. n. with fatal issue can occur.

In our two cases typical outbreaks of iododerma were observed and it seems that iodine has had such an allergen producing effect. Friedberger and Ito, as well



as Jacobs, have shown that rabbit serum given at the same time as iodine can render guinea pigs anaphylactically sensitive to the iodine radical. Rich has recently described a case of hyperthyreoidism in which iodine treatment was continued in spite of symptoms of hypersensitivity to iodine, and this patient developed typical periarteritis nodosa and died.

Our observations teach the importance of being aware of drug allergy, especially in cases of bronchial asthma. Owing to its tendency to bring about irreversible vascular lesions and organic disorders threatening the patient's life, drug allergy is a great danger, if attention is not paid to the warning symptoms in time. If the use of the drug is discontinued promptly, the early vascular lesions of periarteritis nodosa may possibly regress.

### Summary.

Periarteritis nodosa is not as rare as the literature suggests. There is general agreement about the allergic origin of this disease, and it occurs most frequently in persons with allergic tendencies. As neither periarteritis nor nodules are seen in more than a small number of cases, *allergic polyarteritis* would be a more adequate term.

The pathology of the disease is reviewed and some of the clinical and experimental observations which are in favour of its allergic nature are discussed.

Periarteritis nodosa occurs not infrequently in bronchial asthma, and it is then often accompanied by transitory pulmonary infiltrations, leucocytosis and marked eosinophilia, as well as polyneuritis.

A case observed by the author is described: a young woman suffering from bronchial asthma following treatment with potassium iodide developed iododerma tuberosum and a febrile illness with recurrent pulmonary infiltrations, abdominal pain, polyneuritis, leucocytosis and eosinophilia. Biopsy revealed the typical picture of periarteritis nodosa. After the treatment with iodine was discontinued the symptoms disappeared and now (9 months later) the patient is alive and well.

Another woman of 34 years with bronchial asthma and marked eosinophilia presented a similar picture though without polyneuritis, but with cardiac failure and oedema. Following treatment with potassium iodide she also developed iododerma tuberosum, and her condition deteriorated and she died within 3 months. Autopsy revealed no signs of periarteritis nodosa in its earlier stages, but diffuse vascular changes, which resembled arteriosclerosis and consisted of healed endarteritis with thrombosis, especially in the kidneys.

It is therefore concluded that in this second case the patient was suffering from periarteritis nodosa in which the inflammatory changes and the cellular reaction in the arterioles gave way to scar like lesions (fibrosis, sclerosis, canalized thrombi). It is presumed that periarteritis nodosa in the first case was caused and in the second case aggravated by iodine, and in both bronchial asthma formed a previous allergic basis. Drug hypersensitivity in both cases caused iododerma tuberosum.

Owing to its tendency to cause irreversible vascular lesions and organic disorders

dangerous to life drug allergy is a serious danger, especially for asthmatic patients. If the clinical picture of periarteritis nodosa is recognized sufficiently early and the drug discontinued at once, there is a chance that the patient may survive.

### References.

1. Arkin, A.: *Am. Journ. Path.* 6: 401, 1930. — 2. Astwood, cit. Bergstrand, H. (3). — 3. Bergstrand, H.: *Journ. Path. Bact.* 58: 399, 1946. — 4. Bergstrand, H.: *Nordisk Medicin* 3: 2343, 1939. — 5. Blegen, E.: *Tidsskr. N. Lægefor.* 61: nr. 5, 1941. — 6. Broch, O. J.: *Acta Medica Scand.* 113: 311, 1943. — 7. Clark, E., and Kaplan, B. J.: *Arch. Pathol.* 24: 458, 1937. — 8. Cohen, M., Kline, B., and Young, A. M.: *J. A. M. A.* 105: 155, 1936. — 9. Curtis, A. C., and Coffee, R. M.: *Ann. Int. Med.* 7: 1345, 1934. — 10. Dickson: *J. Path. Bact.* 12: 31, 1907. — 11. Engbæk, H. C., Heerup, L., and Thomsen, S.: *Nordisk Medicin* 14: 1535, 1942. — 12. Friedberger, E., and Ito, T.: *Zeitschr. Imm. forsch.* 12: 241, 1912. — 13. Gouley, B. A., and Eiman, J.: *Am. Journ. Med. Sc.* 183: 359, 1932. — 14. Gruber, G. B.: *Virchows Arch. path. Anat.* 258: 441, 1925. — 15. Harbitz, F.: *Norsk Mag. Lægevidensk.* 78: 1051, 1917. — 16. Harbitz, F.: *Ibidem* 82: 609, 1921. — 17. Harbitz, F.: *Ibidem* 87: 854, 1926. — 18. Harbitz, F.: *Nordisk Medicin* 14: 1178, 1942. — 19. Harkavy, J.: *Tr. A. Am. Physicians* 54: 112, 1939. — 20. Harkavy, J.: *Archives of Int. Med.* 67: 709, 1941. — 21. Harris, H. W., Lynch, G. W., and O'Hare, J. P.: *Arch. Int. Med.* 63: 1163, 1939. — 22. Homb, A.: *Acta Med. Scand.* 124: 404, 1946. — 23. Jacobs, J.: *Journ. Immunology* 23: 375, 1932. — 24. Keegan, J. J.: *Arch. Int. Med.* 36: 189, 1925. — 25. Kussmaul, A., and Maier, R.: *D. Arch. klin. Med.* 1: 1866. — 26. Landsteiner, K.: *The Specificity of Serological Reactions*, C. C. Thomas, Springfield, Ill. 1936. — 27. Löffler, W.: *Beitr. Klin. Tuberk.* 79: 368, 1932. — 28. Löffler, W.: *Schweiz. Med. Wschr.* 66: 1069, 1936. — 29. Maier, C.: *Helvet. Med. Acta* 10: 95, 1943. — 30. Metz: *Zieglers Beitr.* 88: 17, 1931—32. — 31. Meyenburg, H. v.: *Schweiz. Med. Wschr.* 23: 809, 1942. — 32. Middleton, W. S., and MacCarter, J. S.: *Am. J. Med. Sc.* 190: 291, 1935. — 33. Olesen, H.: *Nordisk Medicin* 37: 646, 1948. — 34. Opsahl, R.: *Nord. Med. Tidsskr.* 15: 761, 1938. — 35. Rackemann, F., and Greene, J. E.: *Tr. Ass. Am. Phys.* 54: 112, 1939. — 36. Rich, A. R.: *Bull. Johns Hopk. Hosp.* 71: 123, 1942. — 37. Rich, A. R.: *Ibidem* 71: 375, 1942. — 38. Rich, A. R.: *Ibidem* 77: 43, 1945. — 39. Rich, A. R., and Gregory, J. E.: *Ibidem* 72: 65, 1943. — 40. Selye, H.: *J. A. M. A.* 124: 201, 1944. — 41. Svanberg, T.: *Nordisk Medicin* 22: 948, 1944. — 42. Tisell, F.: *Nordisk Medicin* 3: 2345, 1939.

From the Medical Department, Maria Hospital, Helsingfors (Chief: Professor F. Saltzman), and from the Out-Patients Department for Diseases of the Ear, Nose and Throat, Stengård Hospital, Helsingfors (Chief: Docent H. R. Gadolin).

## Multiple Plasmocytoma Treated with Urethane.

### Case Report.

By

FREDRIK SALTZMAN and HENRIK BORGSTRÖM,  
Helsingfors.

(Submitted for publication July 31, 1949.)

---

Plasmocytomas occur mostly as multiple tumours in myelomatosis, but sometimes appear as solitary tumours outside the bone marrow. In myelomatosis the intramedullary tumours are occasionally accompanied by extramedullary growths. If solitary plasmocytoma occurs outside the bone marrow it does so usually in the upper respiratory tract.

Solitary plasmocytoma is sometimes permanently cured by excision, but the prognosis of multiple plasmocytoma is poor and ends in death in about 1—2 years. The disease is characterized by increasing fatigue and cachexia, generally accompanied by severe pain which is sometimes caused by spontaneous fractures in the ribs or in the bones of the limbs.

The treatment of multiple plasmocytoma has so far been unsatisfactory. Because some good results have been obtained in leukemia with urethane, this drug was tried out in myeloma. In their first report on the treatment of leukemia with urethane Paterson et al. (1946) stated that urethane had no effect on myeloma. Alvall (1947) described two patients treated by urethane. In the first there was no response to the drug. In the second who had no pain, the disabling fatigue disappeared, the pathological changes in the blood picture and albuminuria ceased and myeloma cells were no longer seen in sternal marrow, but the skeletal changes were not influenced. Our patient with plasmocytoma who was treated with urethane seemed to improve and the pain, tumours and skeletal changes became less disabling. Although the improvement lasted only for about a year it seems desirable that our observations should be published.

A man of 50 was admitted to Maria Hospital, in Helsingfors, on September 19th, 1946. — In 1930 he had syphilis, treated by 3 series of 10 injections of bismuth and neosalvarsan. After that the W. R. was always negative in the blood

and the cerebrospinal fluid. The patient for a long time was accustomed to heavy drinking. In April 1946 he developed pain in the shoulders, arms and thighs and the pain remained intense in various areas. In May he had pain in the lower parts of the chest on coughing, which improved when a towel was wrapped round his chest. A radiograph taken at the Hospital for Tuberculous Diseases showed no changes in the lungs. In June the left side of the nose became blocked and he bled slightly when blowing his nose. During the summer he noticed tender lumps

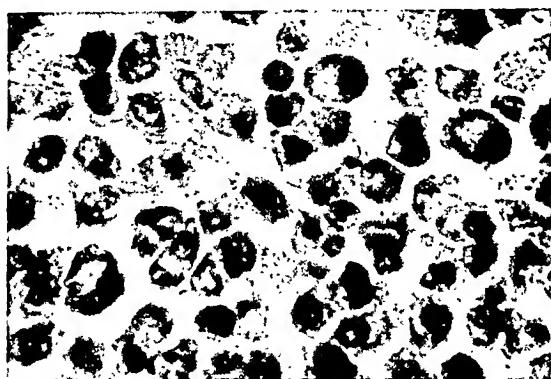


Fig. 1.

of varying size on the chest and also on the head. In August he consulted a doctor who diagnosed bilateral arthritis of the shoulder. He was treated for a fortnight by 6 applications of 130 R. In September he was seen at the out-patients department for diseases of the ear, nose and throat, where the following observations were made: the turbinates and the mucous membrane of right side of the nose were normal; the lower part of the left side was filled by an enlarged inferior turbinate with bluish-red nodules which bled easily. Posterior rhinoscopy showed nothing abnormal. Pharynx and larynx were normal. Biopsy was performed (Borgström) and the tumour (Fig. 1) was diagnosed as a plasmacytoma (Professor A. Saxén). The patient was sent to Maria Hospital for further examination.

Radiographic changes were found in the skull, ribs, left clavicle, femora, hip bones and in the left humerus which also showed a spontaneous fracture. The changes in the skull were typical (Fig. 2) and on palpation there were firm, protruding lumps, 2 the size of a walnut and several smaller ones. The acromial end of the clavicle was thickened and there were a number of tender nodules attached to the ribs.

There was no enlargement of the spleen or the lymph glands. The blood picture and the sternal marrow which was examined repeatedly were normal. The sedimentation rate was 71 mm in 1 hour, despite the absence of fever. The formol-gel and Takata tests in serum were negative. Plasma proteins varied between 6.5 and 8.1 per cent.

Urethane treatment was started on September 30th with 3 daily doses of 1.5 g in 10 per cent solution and continued for a month. After an interval of a month another course was given from November 29th to January 8th, but discontinued

on account of the patient's indisposition. A further course with a smaller dose, 1.5 g daily, was given from February 10th to May 5th.

After 10 days of treatment the nodules on the skull became smaller and another 10 days later they disappeared completely, and distinct depressions developed gradually at the site of the former nodules.

The improvement was also appreciable in the radiographs (Figs. 2 and 3).



Fig. 2.

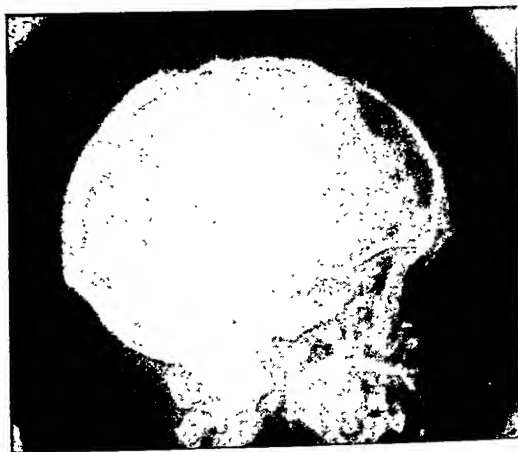


Fig. 3.

At the beginning of November the pain ceased almost completely and at the same time the nasal tumour decreased in size. In December it was only half its former size and breathing through the nose became easy and remained so. After another month only small remnants of the tumour were seen on the inferior turbinate. — The sedimentation rate decreased gradually, in December it was 8 mm in 1 hour and returned to the normal value of 3 mm in 1 hour in January.

On March 8th the patient was discharged from the Hospital. Treatment was continued during the summer and small doses were given for several short periods. The patient felt well and was able to carry on his work in a factory.

In September 1947, *i. e.* after a year on urethane severe sciatic pain developed on the left side. The bones of the skull were normal on radiographs but there was increased destruction of the femora and hip bones on the left side. A firm fixed tumour became palpable above the left clavicle and there were several small tumours in the abdominal wall. Urethane treatment with daily doses of 4.5 g for 1 month did not influence the tumours or the pain, and the patient refused to continue with the treatment. He was readmitted to Hospital. After the courses of urethane a trial was made with radiotherapy from November 27th to December 17th, but without result. Stilbamidin was not used as it was not obtainable at that time.

On November 3rd, 1947 Dr. Raekallio kindly analysed the plasma proteins and reported as follows:

Total proteins 7.40 per cent (micro-Kjeldahl method).

Electrophores.: Albumin 3.46 per cent.

Globulins 3.94 per cent.

$\alpha$ -globulin 0.44 per cent.

$\beta$ -globulin 1.80 per cent.

$\gamma$ -globulin 1.70 per cent.

Albumin-globulin quotient 0.87.

Though the total plasma proteins were normal, there was hyperglobulinemia, both relative and absolute, due to an increase in the  $\beta$ - and  $\gamma$ -globulins, and in  $\beta$  there was on the negative side a strong  $\beta$ -anomaly.

The formol-gel test which in November 1947 was still negative, became positive in December and Bence-Jones' proteose appeared in the urine. The sedimentation rate increased and rose gradually to 136 mm in 1 hour. The blood picture altered only slightly although urethane is considered to be a cell poison affecting cell-division. Thrombocytopenia of 62,000 platelets was observed during the early part of urethane treatment, but after its cessation the platelets were once again normal in number and there was no further attack of platelet deficiency. There was no leucopenia or granulocytopenia, and no anemia except during the last month when moderate normochromic anemia with normal leucocyte and platelet counts developed. During the last few months the patient was often troubled by diplopia when looking to the right. The optic fundi were normal.

The patient died on January 11th, 1948. Unfortunately autopsy was refused, but some of the tumours were excised. The tumour above the left clavicle and one in the abdominal wall were plasmocytomas of the same histological structure as the original nasal tumour. In pieces of mucous membrane from the left middle turbinate very many plasma cells were found.

### Summary.

A patient with multiple plasmocytoma was treated with urethane. The diagnosis was confirmed but the effect of urethane is still not certain. Shortly after the start of treatment with urethane distinct and rapid improvement occurred

which lasted for 1 year, but later the patient's condition deteriorated. The duration of the illness (21 months) was not unusually long. Whether the distinct improvement in the case described was incidental or was due to the treatment, cannot be ascertained on the basis of one single case especially as spontaneous remissions in myelomatosis are known. It is, however, important to try even the slightest palliative possibilities in a disease so utterly hopeless and painful as multiple myelomatosis.

#### References.

Alvall, N.: Svenska Läkartidn., 1947: 44: 28. — Paterson, E., Haddow, A., Ap Thomas, I., and Watkinson, J. M.: Lancet, 1946: I: 677.

---

From the Bispebjerg Hospital Med. Dept. C, Copenhagen.  
(Chief phys.: Professor K. Secher, M. D.)

## Basophilic Stippling of the Red Blood Corpuscles during Chrysotherapy.

By

HEMMING ENGELUND POULSEN.<sup>1</sup>

(Submitted for publication August 4, 1949.)

In the treatment of polyarthrititis with gold preparates, there is still a certain risk of complications, which may impede the carrying out of the treatment. No doubt the risk of complications will in the first place depend on which preparates are used, a thing that can be seen from the fact, that even severe complications may arise from the administering of very small doses of some special preparate, whereas other preparates may be given in bigger doses without inconvenience.

This applies to Sanocrysin, which in the majority of cases can be given without inconvenience in doses varying from 1—1.5 grammes. When Snyder and Trayer relate a case of dermatitis after 15 milligrams of Sanocrysin, it must be supposed that the preparate administered was not of Danish origin.

In this connection it must, as Secher has stated, be stressed how inconsequent it is after all to talk about treatments with gold in general, when as a matter of fact the various preparates differ so widely in their toxic effect. Experiences and results obtained by using different preparates cannot be compared inter se.

But even the Sanocrysin preparate may cause complications. From a practical point of view, however, these disturb but little the routine work of the treatment as it is carried out in department C of Bispebjerg Hospital. Dermatitis is the only exception, but even this complication appears to be losing in importance as it has now become possible to give B. A. L. (dimercaptopronal, Danish preparate: Antoxol), thus erythems may be hindered from developing into dermatitis, which up till now happened in a number of cases, a consequence utterly disagreeable to the patient. The dermatitis was not fully developed until after some six weeks.

Until now it has not been possible to tell in advance which patients were in danger of getting complications, however these will be explained. Neither »experimental doses» nor cutaneous injections show anything.

This is the reason why new reports are studied with such keen interest. This also applies to a work by Parr and Shipton from 1947, about »Basophilic stippling of the red corpuscles with special reference to its occurrence during chrysotherapy».

<sup>1</sup> Arvevej 13, Haslev (Denmark).





Table 1.

Table for patients treated with Myocrysin (Au 50.53 %).

	Age	Sex	Hb %	Eryt. mill. per mm <sup>3</sup>	Leuc.	neu.	eo.	bas.	lym.	mon.	Bas. st. Eryt pr million	Reac.	Acc. eff.	Dosage	SR. mm
1	63	f.	74	4.05	6,000	66	3	0	23	8	350	pains	0	6 × 5 cgr	84
2	61	—	96	4.38	5,420	50	2	1	40	7	450	—	—	—	18
3	78	—	77	4.11	4,210	61	3	0	29	7	200	—	—	—	63
4	82	—	82	4.28	5,140	58	7	—	30	5	400	—	—	—	83
5	71	—	89	3.40	1,640	68	4	—	26	2	250	—	—	—	55
6	44	—	71	3.49	5,280	61	4	—	30	5	600	—	—	—	90
7	61	—	92	4.49	4,210	60	7	—	37	6	150	—	—	8 × 5 cgr	42
8	50	m.	88	3.60	3,540	73	2	—	21	4	200	—	—	6 × 5 cgr	51
9	49	f.	82	3.67	4,200	67	8	—	19	6	100	0	—	—	45
10	50	—	84	3.54	3,920	70	6	1	20	3	350	0	—	—	61

The diagnosis for all the patients was: Polyarthrits chr. progr.

Table 2.

Table for patients treated with Sanocrysin (Au 37.46 %).

	Age	Sex	Hb %	Eryt. mill. per mm <sup>3</sup>	Leuc.	neu.	eo.	bas.	lym.	mon.	Bas. st. Eryt pr million	Reac.	Acc. eff.	Dosage	SR. mm
1	20	m.	100	4.72	6,320	51	1	0	45	3	1,250	pains fever	exant.	50, 65, 50, 65, 65 cgr	72
2	61	f.	88	3.65	4,300	50	12	—	33	4	300	pains	0	50, 65, 65, 75, 75 cgr	42
3	58	—	98	4.39	5,000	50	3	—	40	7	200	pains	0	65, 65, 75, 75 cgr	60
4	55	—	76	3.80	3,760	62	0	—	36	2	850	pains fever	0	35, 35, 50, 50 cgr	77
5	43	—	85	3.95	4,880	60	2	—	35	2	1,500	pains fever	exant.	35, 50, 50, 50, 65 cgr	68
6	63	—	87	4.45	5,920	74	1	—	25	0	450	pains	diarr.	33, 35, 50, 50 cgr	42
7	17	—	88	4.40	6,040	70	9	—	19	2	200	pains	0	35, 35, 50, 50 cgr	35
8	42	—	100	4.48	4,480	60	9	—	37	4	400	pains	thromb. penia	50, 50, 50, 65, 65 cgr	23
9	39	—	61	3.62	4,280	58	3	—	35	4	900	pains	0	35, 50, 50, 65, 65 cgr	67
10	51	—	78	3.74	8,420	76	2	—	19	3	1,450	pains fever	dermat.	35, 50, 50, cgr	38
11	43	—	76	3.67	4,900	64	8	1	24	3	800	pains	0	35, 35, 50, 50, 65 cgr	64
12	47	—	82	3.95	5,360	72	6	1	15	6	650	pains	0	50, 50, 50, 65, 75 cgr	56

The diagnosis for all the patients was: Polyarthrits chr. progr.

## II. Patients Treated with Sanocrysin.

The application of Sanocrysin has been carried out in accordance with the procedure worked out by Secher in 1936.

In most cases the initial dose has been 35 centigrammes increasing to 50 centigrammes in the second and third injection ending with 65 to 75 centigrammes in the fourth and fifth.

The twelve patients mentioned in the table were specially selected cases where the accessory effects of the Sanocrysin were particularly strong.

As the tables show three patients got exanthema, 1 thrombopenia and 1 diarrhoea.

Along with Sanocrysin these patients have received preparates containing vitamins A, B and C.

As mentioned above, the counting of the basophilically stippled red corpuscles took place regularly and it was found that the accessory effects pronounced themselves at an earlier stage than the increase of the basophilically stippled erythrocytes. Consequently the counting of these erythrocytes cannot show whether the patient is particularly sensitive to Sanocrysin or not.

The tables show that the three patients who got exanthema all had more than 1 promille of basophilically stippled erythrocytes, whereas the patient with thrombopenia and the patient with diarrhoea had 0.4 promille and 0.45 promille respectively, while a patient who reacted only slightly had 0.9 promille.

Besides these not very convincing figures, the uncertainty of the method of measuring and the fact that it is a very prolonged and tedious process must be taken into consideration.

### Summary.

When patients are treated with Sanocrysin the number of basophilically stippled erythrocytes will sometimes, but not always, be correlated to the intensity of the accessory effects. This fact together with the objections made above leads to the conclusion, that the counting of the basophilically stippled red corpuscles may be abandoned as part of the routine examinations made when diseases are treated with the preparate in question. Moreover as the increase in the number of basophilically stippled erythrocytes will not prove itself until after the complications have pronounced themselves. This reaction cannot give any indication as regards the best way of employing the treatment so that complications may be avoided.

### References.

1. Heinild: Undersogelser over de kvantitative Variationer i Blodpladeantallet. København 1942. — 2. Mollgaard, H.: Chemotherapy of Tuberculosis. Copenhagen 1927. — 3. Parr, L. J. A. and Eva Shipton: Basophilic Stippling of the red Corpuscles with special reference to its occurrence during Chrysotherapy. The med. journ. of Australia. 1 P 193. 1947. — 4. Secher, K.: Directions for the treatment of Rheumatic Joint diseases Copenhagen 1946. (Lit.). — 5. Secher, K.: The theoretical Basis of the treatment of Tuberculosis and Polyarthrititis with Sanocrysin. Copenhagen 1947. — 6. Snyder, R. G., C. Tragger and C. M. Kelly: Ann. of int. Med. 12. 1672. 1939.

From the Department of Medical Chemistry, University of Helsinki.

## On Hyaluronidase Inhibitors in Human Blood.

By

EINO KULONEN.

(Submitted for publication August 5, 1949.)

Factors which inhibit hyaluronidases in the blood, have received interest during recent years as it has become increasingly apparent that hyaluronic acid plays a part in the physiology and pathology of connective tissue, though so far our knowledge of this part is limited. Another approach to this question is opened by the hypothesis that hyaluronidase takes part in the spread of bacterial infections in the animal organism. So far the work on hyaluronidase inhibitors has been the only connection between experiments on these substances and clinical practice.

Already in 1932 an antitesticular serum inhibiting the »spreading factor» was discussed by Duran-Reynals (1932) and it was found that hyaluronidase injected into the blood rapidly disappeared from it (Duran-Reynals, 1933). The hypothesis of inhibitors obtained by immunisation with hyaluronidase was confirmed subsequently by McClean (1942). At the same time it was found that some substances which chemically resemble hyaluronic acid exert an inhibitory action on hyaluronidases, whereas for instance polysaccharide of blood group A and the Shiga-Kruse polysaccharide are ineffective in this respect. At that time a common inhibitor in the blood of the »diffusion factor» was discussed by Humphrey (1943), and it was stated that serum inhibits the dispersing action of hyaluronidase upon follicular cells (Leonard and Kurzrok, 1946).

About bacterial hyaluronidases in particular it was noted that serum contained antibodies against these enzymes, but it was generally believed that they were derived from specific immunisation (Hobby et al. 1941; McClean et Hale, 1941; Duran-Reynals, 1936, 1942). More recent studies were stimulated by observations made by Haas (1946), who stated that a special system of enzymes exists which exerted an influence upon the course of infection in the organism. He supported the idea that serum contained a non-specific factor of the nature of enzymes, which he called anti-invasin and which inhibited the bacterial invasin (hyaluronidase). He found that it was thermolabile and that it was inactivated by phosphates. He claimed that bacteria and animal poisons possessed a proinvasin which counteracted this substance and that the pro-invasin in turn was inactivated



the original enzyme to which serum has not been added. The use of standard time benefits large test series. The amount of enzyme to be used is that which depolymerizes the hyaluronic acid to a point near the turbidimetric minimum. An excess should be avoided.

### Tests.

The following substances are pipetted into a test tube:

0.25 ml of 0.85 per cent sodium chloride solution,

0.03 ml citrate plasma

0.02 ml of enzyme solution.

The pH is then 7.05 and the mixture is allowed to stand at room temperature (18° C.) for 15 minutes, after which 0.25 ml of hyaluronic acid solution is added. The pH is then 5.95. The mixture is stirred and placed in a water thermostat at 37° C. for 30 minutes after which the remaining enzyme is inactivated by placing the mixture in a water thermostat at 56° C. for 10 minutes. When the mixture is cooled, 3 ml of serum dilution (consisting of 2.90 ml of 0.5-mol. acetate buffer solution at pH 3.8 and of 0.10 ml of sterile serum) is added for the turbidimetric determination of the amount of residual hyaluronic acid. Photometric determination is made exactly 5 minutes later (filter S 61). In order to obtain identical conditions the same batches of solution were used and double determinations were made. No preserving substances were used.

### Solutions.

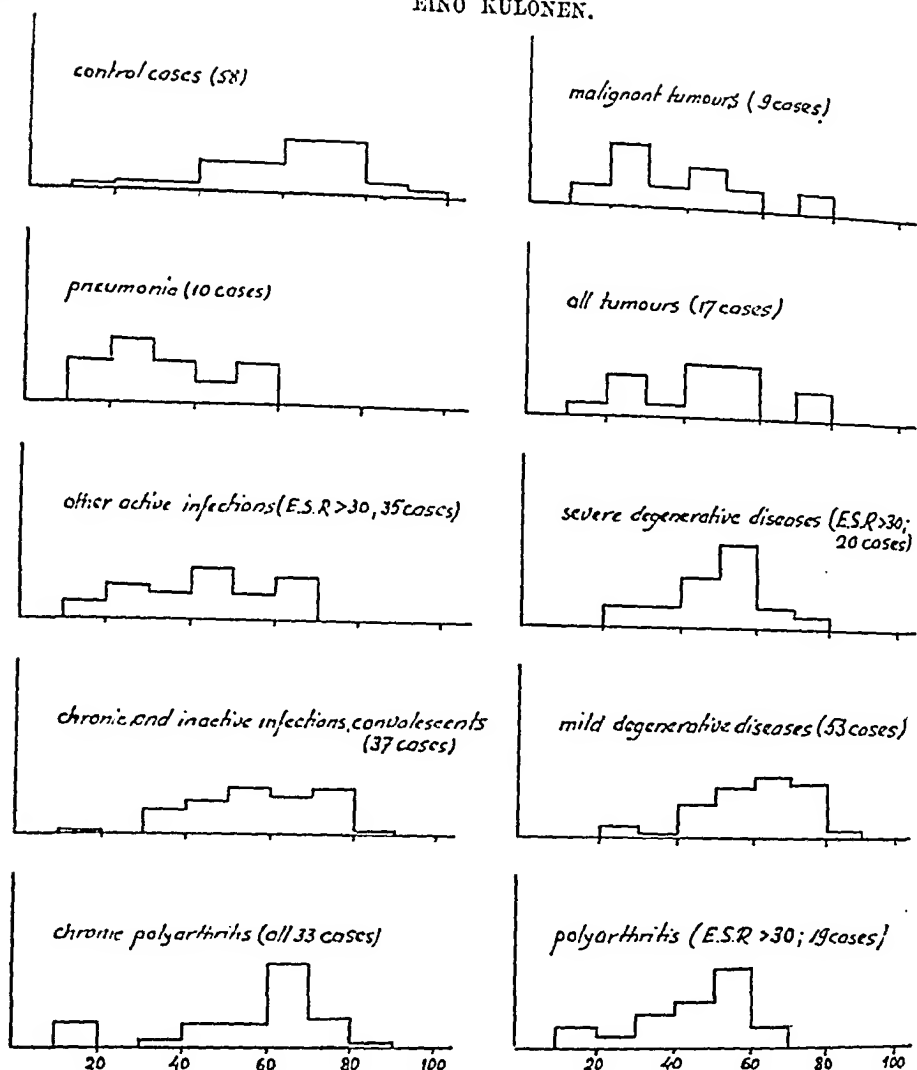
The enzyme solution was made from a 24-hour old streptococcal culture (group A, type 4, strain H713)<sup>1</sup> grown in Gladstone-Filde's casein-hydrolysate-yeast medium. The precipitate by  $\frac{2}{3}$ -saturation with ammonium sulphate was purified further by adsorption by Rogers' method to ferric hydroxide and by elution with sodium carbonate. For preservation the resulting solution was dialysed against glycerine. The solution used in tests was a dilution with 0.85 per cent sodium chloride in the ratio 2 : 5, containing 0.26 mg nitrogen per ml.

The hyaluronic acid solution contained 0.1 per cent of substance prepared from umbilical cord and 0.9 per cent sodium chloride and was buffered at pH 5.6 with  $\frac{2}{15}$  mol. phosphate buffer. Umbilical cords dried in acetone were extracted with 1 per cent sodium chloride solution, precipitated 2—3 times with alcohol and treated by shaking with a chloroform-amylalcohol mixture to eliminate any protein. The final steps were double precipitation with alcohol, washing with acetone and ether and quick drying in the thermostat at 37° C.

### Results.

Certain observations about this method should first be made. The use of citrate plasma is possible for the test. Contrary to earlier statements, sodium citrate content

<sup>1</sup> Dr. H. J. Rogers of the University of Leeds kindly supplied this strain.



Distribution of Cases in Certain Diseased Conditions according to the Inhibitory Action of Plasma. (Figures indicate per cents of non-inhibited hyaluronidase.) E. S. R. = Erythrocyte Sedimentation Rate according to Westergren.

of 0.78 per cent, is not excessive for use under the conditions described above. 0.30 ml of plasma proved sufficient. Storage in the refrigerator at 4° C. for 8 days did not produce any marked change. An effort to inactivate plasma by keeping it at a temperature of 56° C. for 10 minutes decreased its inhibitory power only slightly. As regards the effect of temperature and time upon the reaction between the plasma and hyaluronidase, the reaction was found to occur at any temperature between 4° C. and 37° C. In the range of 18° C. to 37° C. in particular the difference in the temperature produced only a slight effect. The greater part of the reaction occurs within 15 minutes but continues slowly after that.

The results obtained by investigation of patients are seen from the graphs, which show the distribution of the cases. The more cases there are to the left, the greater the inhibitory action of the plasma upon the hyaluronidase. The figures

give the percentages of non-inhibited hyaluronidase concentration. In about 30 cases two determinations were made with plasma which had been kept for 10 minutes at 56° C., but the slight decrease in the action was common to all the groups. The control material consisted of patients who have not been included in the other groups, mainly psychiatric cases or of disorders of the digestive tract and of the blood. Cases of hormonal disorders were so few, that they have not been separated. Opinions vary as regards the subdivision of degenerative conditions to mild and severe, the latter only including cases with a high mortality rate, *i. g.* infarcts, strokes.

### Discussion.

These tests may be criticized on the grounds that they are not fully comparable to biological conditions. This, of course, cannot be denied. It may be claimed that the hyaluronic acid preparation used lost its biological activity at least from the serological point of view, but we do not know as yet what importance this has and cannot determine it. Considering that the enzyme is not uniform, it is apparent that we are dealing here only with fragments of total phenomena. As the turbidimetric method used in the determination of the substrate is based on high polymerisation we must admit that tests of this kind will answer the question of the amount of substances present in the plasma which act as inhibitors upon those enzymes which depolymerize tissue polysaccharides and particularly hyaluronic acid. This is quite sufficient as far as the action of hyaluronidase upon infection by this mechanism is concerned, but the findings may nevertheless be erroneous as the hyaluronic acids in various organs probably differ from each other as regards the speed of their enzymic depolymerisation and as the preparation used in the *in-vitro* experiments undoubtedly is different. The speed of turbidimetrically measured depolymerisation essentially depends on the molecular weight which is lowered by the preparation. There may also be reason to refer in this connection to the opinion which regards toxins, however, as the most important factor in the spreading of infection in the animal organism (Hechter and Solomons, 1948).

This action is indicative of a common defence reaction but hyaluronidase inhibition as such may not be of great physiological importance. The inhibition may be caused by substances in the blood which may exert a similar non-specific action upon hyaluronidase as do certain polysaccharides, for instance heparin. This opinion is supported by the relatively great thermostability of the inhibitor and the marked independence of the reaction from temperature.

Tests with plasma from patients suffering from various diseases indicate that the inhibiting factor is non-specific, in fact, it is not even associated with infections alone, although it is most active in those cases. It is interesting that in *B. coli* and tuberculous infection this inhibiting factor is not much increased. Rheumatoid arthritis does not occupy a special position and the slight increase which occurs in its active phase may be due to the infection itself. The reason for the increase of the inhibitor in malignant tumor cases is not yet known. In some cases at least, the carcinoma cells may contain substances possessing the action of



hyaluronidase but there is no definite reason to assume the presence of antibody. It is also difficult to account for the increase of these factors in severe conditions of degenerative origin, but they are often accompanied by infections and absorption.

It is our opinion, that there is every reason to support the hypothesis that we are dealing here with a substance which is possibly a carbohydrate complex, already physiologically present in the blood. In this connection the increase of albumin sugar in some diseases and Glick's observation, that the inhibitor accompanies albumins in the electrophoresis are interesting. We have, however, no definite knowledge of the chemical character of the inhibitor.

It is hazardous to draw any conclusions in this complicated question, but it may be that we are dealing here with a part of a general defensive reaction of the animal organism, even if there is for the present uncertainty about the importance of the hyaluronidase inhibition as such.

A comparison with the erythrocyte sedimentation rate and with acute phase protein (Hedlund, 1947) comes to mind and continued studies may in time produce information on the physiological significance of this action.

### Summary.

A method for the determination of the hyaluronidase inhibitor in plasma is described. A citrate content of 0.78 per cent is not deleterious. In test conditions the inhibitor was fairly stable at 56° C.

In about 300 cases the faculty of the plasma to inhibit streptococcal hyaluronidase was tested and found increased in acute infections and particularly in pneumonia. In rheumatoid arthritis, the increase was not greater than in infections in general. In malignant diseases a marked increase was also seen and the same was true in severe degenerative diseases. No differences were found in the thermostability of the plasma in different conditions.

The importance of this inhibitor is discussed.

Financial support from the Nordisk Insulinfond is gratefully acknowledged.

### References.

- Adner, P. L.: *Upsala läkaref. förh.*, 1948, 53, 39. — Baumberger, J. P. and Fried, N.: *J. Biol. Chem.*, 1948, 172, 347. — Dorfman, A.: *J. Biol. Chem.*, 1948, 172, 377. — Dorfman, A., Ott, M. D. and Whitney, R.: *J. Biol. Chem.*, 1948, 174, 621. — Duran-Reynals, F.: *J. Exper. Med.*, 1932, 55, 703. — Duran-Reynals, F.: *J. Exper. Med.*, 1933, 58, 161. — Duran-Reynals, F.: *J. Path. Bact.* 1936, 42, 477. — Duran-Reynals, F.: *Bact. Rev.*, 1942, 6, 197. — Friou, G. J. and Wenner, H. A.: *J. Infect. Dis.*, 1946, 80, 185. — Fulton, J. K., Marcus, S. and Robinson, W. D.: *Proc. Soc. Exp. Biol.* 1948, 69, 258. — Glick, D. and Moore, D. H.: *Arch. Biochem.* 1948, 19, 173. — Glick, T., Good, T. A. and Bittner, J. J.: *Proc. Soc. Exp. Biol.* 1948, 69, 524. — Haas, E.: *J. Biol. Chem.* 1946, 163, 63, 89, 101. — Hadidian, Z. and Pirie, N. W.: *Biochem. J.* 1948, 42, 266. — Hechter, O. and Solomons, S.: *Nature*, 1948, 162, 701. — Hechter, O. and Scully, E. I.: *J. Exper. Med.* 1947, 86, 19. — Hedlund, P.: *Acta Med. Scand.* 1947, Suppl. 196, 579. — Hobby, G. L., Dawson, M. H., Meyer, K. and Chaffée, E.: *J. Exper. Med.* 1941, 73, 309. — Humphrey, J. H.: *Biochem.*

J. 1943, 37, 177. — Leonard, S., and Kurzrok, R.: *Endocrinology*, 1946, 39, 85. — McClean, D.: *J. Path. Bact.* 1942, 54, 284. — McClean, D. and Hale, C. W.: *Biochem. J.* 1941, 35, 159. — Quinn, R.: *J. Clin. Invest.* 1948, 33, 471, 477. — Rogers, H. J.: *Biochem. J.* 1948, 43, 633. — Thompson, R. T.: *J. Lab. Clin. Med.* 1948, 33, 919. — Thompson, R. T. and Moses, F. E.: *Federation Proc.* 1948, 7, 282. — Thompson, R. T. and Moses, F. E.: *J. Clin. Invest.* 1948, 27, 805.

---

From the Medical Out-Patients Department, the Kommunehospital, Copenhagen.  
(Director: Dr. P. Schultzer, M. D.)

## The Significance of the Exton-Rose Tolerance Test for the Diagnosis of Diabetes Mellitus.

By

VAGN SCHMIDT.<sup>1</sup>

(Submitted for publication August 7, 1949.)

In 1946 Schmidt and Christensen compared the value of the glucose tolerance test as carried out according to Exton and Rose (1931, 1934) with the standard test commonly used in this country (one dose of 70 g glucose dissolved in 500 g water by mouth; blood sugar estimations for 3 hours at intervals of 15 minutes; urine tests 1, 1½ and 2½ hours after the test dose). They concluded from these investigations that the Exton-Rose test is just as satisfactory as the standard test, which is far more troublesome for both patient and examiner. Patients known to be diabetics and some believed to be normal were selected for the experiments. The Exton-Rose test proved to be a useful one for both groups, and even where the standard test revealed a latent diabetes as in a number of patients with hyperthyroidism it gave the same results as the standard test. The authors tried to establish criteria for the tolerance tests on the basis of their experience.

The object of this paper is to investigate whether the Exton-Rose tolerance test has answered expectations in clinical practice. For this purpose the results of routine Exton-Rose tests carried out on patients who attended the Medical Out-Patients Department during 1946—1949 were analysed.

Exton and Rose named their test »the one hour two-dose dextrose tolerance test». It is based on Allen's (1913) paradox: »the more sugar is given the more is utilized», also referred to as the Hamman-Hirschman or Staub-Traugott phenomenon. Instead of given glucose in one dose, as for the standard test Exton and Rose give 2 equal portions with an interval of 30 minutes. The first dose of glucose stimulates the insulin-glycogen mechanism to activity so that the body can normally deal with any amount of glucose without developing hyperglycaemia. Diabetic patients react with distinct hyperglycaemia because the insulin-glycogen

<sup>1</sup> Classensgade 59, Copenhagen.



it is difficult to avoid the inclusion of a few of »latent» diabetes. This will of course tend to increase the upper limit of »normal».

By a study of the tolerance test as used in clinical practice with the criteria stated we may obtain better definition and thereby reduce the number of doubtful diagnoses. This has been attempted by an analysis of the following series.

### Original Investigations.

Since Schmidt and Christensen's paper the Exton-Rose tolerance test has been used as the standard method for the diagnosis of diabetes mellitus in the Medical Out-Patients Department of the Kommunehospital. The test was used only where it was impossible to make a diagnosis in the usual way by physical signs and symptoms, and increased fasting blood sugar, glycosuria etc. The procedure followed has been mentioned above and included blood sugar estimations on capillary blood according to Hagedorn-Jensen. These tests have not given the laboratory staff any extra work, but they have the advantage that the patients are informed of the results on the same day. The test was commenced at 8 a.m. and concluded already at 9 a.m.

54 patients were examined and 14 of these were declared non-diabetics. These patients had been referred on account of various suspicious signs and symptoms such as fatigue, polyuria, furunculosis and incidental findings of sugar in the urine etc. These results of the tolerance tests have been set out in *table I*.

These 14 patients were all definitely non-diabetics and no further comment is required.

Table II shows the results for 6 patients tested on account of glycosuria found accidentally or signs and symptoms caused by glucosuria (polyuria, pruritus vulvae, catarrhal urethritis etc.) They were found not to suffer from diabetes mellitus, but from benign glycosuria due to a low sugar threshold. If the threshold is very low, glucose is found also in the first sample of urine, but usually only in the second.

Case 5 was the only one with a third blood sugar value high enough to suspect a latent condition. The patient had, however, no complaints pointing to diabetes. He was seen in the Out-Patients Department on account of cardiac pains and a routine examination of the urine revealed glycosuria.

Case 4 was also submitted to the standard tolerance test, which showed a maximum blood sugar of 166 mg%, and a normal curve. There was sugar in the two later samples of urine and this test therefore gave the same result as the Exton-Rose test, *i. e.* benign glycosuria due to a low sugar threshold.

For the 6 cases shown in Table II the results of the Exton-Rose tolerance tests were of decisive importance for the diagnosis.

Five patients' glycosuria was discovered by routine examinations during pregnancy. They were therefore examined for diabetes mellitus. The fasting blood sugar was normal in all and Exton-Rose tolerance tests showed results as shown in Table III.

In case 3 glycosuria had been discovered during the second month of pregnancy, but the patient miscarried shortly after, and the Exton-Rose tolerance test made then gave normal readings. In all the other patients glycosuria had been discovered by routine urine analysis during pregnancy.

During pregnancy a lower sugar threshold is physiological and glycosuria is fairly common, but pregnancy very rarely causes manifest diabetes. During the child bearing period only about 5 % of women develop diabetes during pregnancy (P. White, 1946). The finding of glycosuria should make the physician very careful in his examination of the pregnant woman and the possibility of diabetes mellitus should be kept in mind, because correct treatment is of great importance for both mother and child.

It appears from Table III that 3 of the 5 patients were certainly not diabetic (cases 1, 3 and 5), while the remaining 2 presented values within the «uncertain range». Such patients should, therefore, be kept under observation; the test should be repeated in the puerperium and again after weaning. Furthermore, the patients presenting such results in the Exton-Rose test should avoid sugar and reduce their carbohydrate intake.

The importance of a tolerance test for the diagnosis of diabetes mellitus is obvious for the group of diabetics who present a normal fasting blood sugar. Such a series has been collected in Table IV. They were patients in whom glycosuria or other physical signs of diabetes mellitus had been discovered. In some of them increased fasting blood sugar values had been found which during the treatment (restriction of carbohydrates and reduction of calories — often advised for obesity) had fallen to normal limits, while at the same time glycosuria had often subsided.

As appears from Table IV the Exton-Rose tolerance tests were of decisive diagnostic importance in these patients. All the tests showed definitely abnormal values, no matter which criteria were used. In these patients the results of the glucose tolerance tests showed the necessity of a regime of reduction of weight, when obesity was present. Increasing obesity is generally associated with a corresponding exacerbation of diabetes, which may then often declare itself. Loss of weight, on the other hand, is often accompanied by an almost parallel improvement of diabetes.

In other cases the Exton-Rose tolerance test was carried out even if it was not strictly necessary, most often on patients who were referred to the Out-Patients Department with vague symptoms. The first examination may have revealed glycosuria, and the Exton-Rose test was therefore ordered. It showed an increase in the fasting blood sugar value and correspondingly considerable rises in the sugar values at the second and third estimations. Table V shows the results in patients with manifest diabetes.

It appears that in both these groups the second glucose dose in the Exton-Rose test has caused a further rise in the blood sugar, except in two patients (cases 4 and 13 in Table IV), but in these 2 cases the third blood sugar estimation was as high as, or only a little below the second. The lowest value for the third blood sugar value was 194 mg% (case 4, Table IV), but the rise from the first to the second blood sugar estimation amounted to 85 mg%, and there was sugar in the

second sample of urine. This patient therefore must be regarded as diabetic according to Exton and Rose's criteria.

Four other patients were examined by the Exton-Rose tolerance tests and their results are indicated in Table IV. These cases are designated «uncertain», because it was impossible to make a diagnosis on the basis of the Exton-Rose test alone.

Cases 1 and 2 (Table VI) must be regarded as benign glycosuria as there were no other signs of diabetes. Case 2 was not classed as a diabetic, in spite of the considerable rise in blood sugar from the first to the second estimation (93 mg%) because this rise was followed by a marked fall from the second to the third blood sugar estimations and because the margin of error of blood sugar estimations may be very great. Cases 3 and 4 may perhaps be designated diabetes mellitus. In case 3 the marked rise in the first phase and the slight fall in the second suggest the diagnosis. In case 4 the high fasting blood sugar level almost certainly settled the diagnosis. However, in these 4 cases it seemed advisable to repeat the tolerance tests later and to keep the patients under observation until the diagnosis could be finally settled one way or the other.

To give an impression of the various curves obtained some of the typical ones from the various groups are shown in Fig. 1.

The Tables show that the third blood sugar level did not exceed 150 mg% in «normal» subjects (Table I) nor 159 mg% in patients with renal glycosuria. On the other hand, the third blood sugar level was more than 194 mg% in all definite cases of diabetes. Of the group of «pregnant» (Table III) and «uncertain» (Table VI) the patients whose third blood sugar level was above 180 mg% were probably diabetic, but the other patients in these «doubtful» groups did not exceed 150 mg% in their third blood sugar values. The following criteria are therefore suggested:

(1) *Normal*: patients with a third blood sugar level below 160 mg% and no glucose in the first and second samples of urine.

(2) *Diabetes*: patients whose third blood sugar level exceeds 180 mg%, or lies between 160 and 180 mg%, while the rise from the first to the second estimation exceeds 75 mg%, or is accompanied by an abnormally high fasting blood sugar level.

(3) *Benign glycosuria*: patients with sugar in the first and for second samples of urine, but with a normal blood sugar curve.

(4) *Doubtful*: patients whose third blood sugar level is between 160 and 180 mg%, where the rise from the first to the second estimation does not exceed 75 mg%.

It appears that by these criteria all the patients in the series described here may be classed in one or other group, but investigations on much larger series will be necessary before such criteria can be finally decided. There will probably always be some cases where the diagnosis cannot be made by the Exton-Rose test alone. As in all other diagnoses we should never be content with one form of investigation. The diagnosis must always be based on the physical signs as well as on the results of laboratory investigations and not alone on one or the other.

During the 3 years the Exton-Rose tolerance test has been used it has, however,

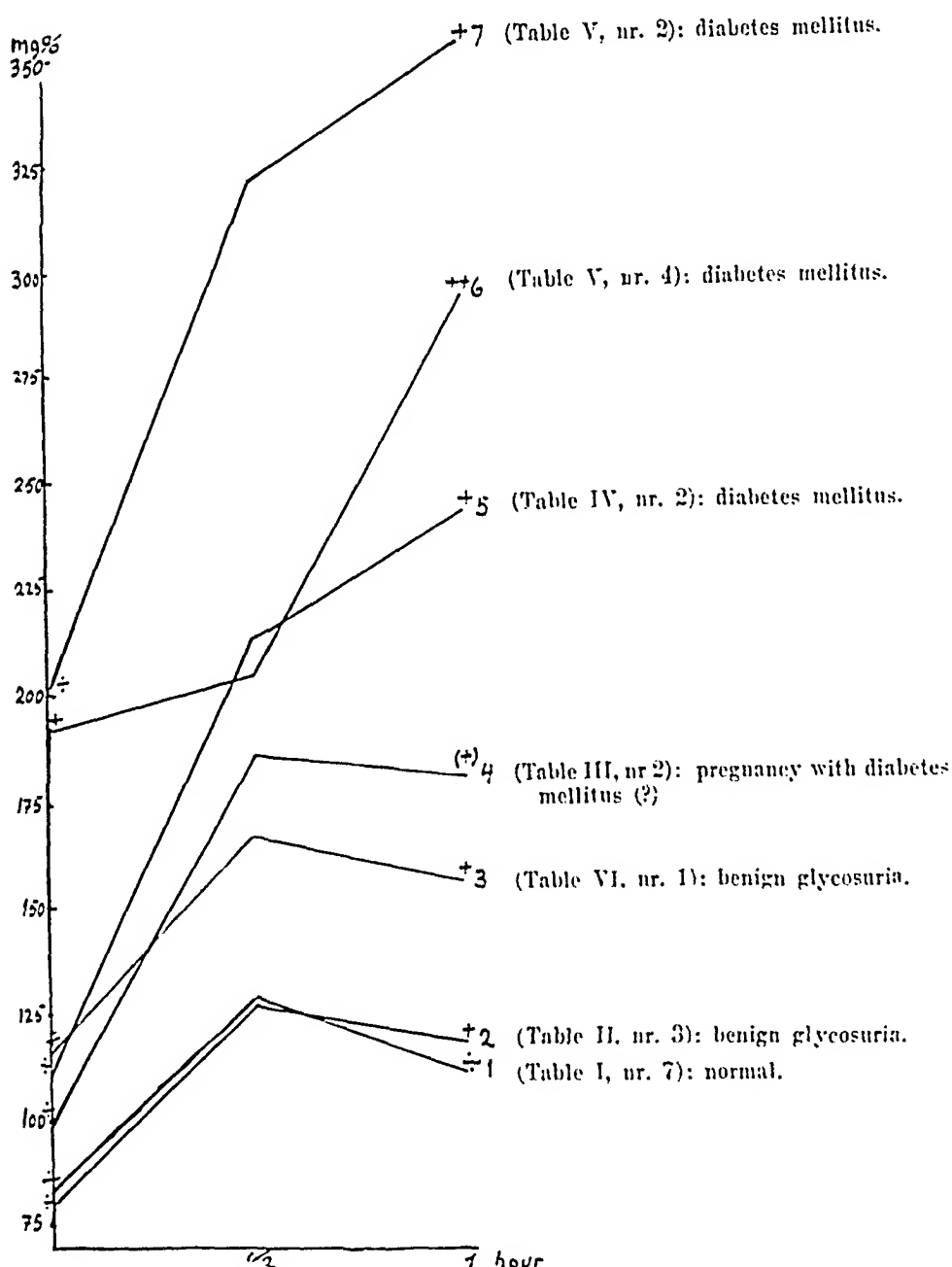


Fig. 1. Blood sugar values with the Exton-Rose procedure.

÷ or — means presence or non-presence of glucose in the urine samples.

proved to be of such value, that we confidently suggest it to other workers. In particular it is useful for Out-patients whose symptoms demand a glucose tolerance test. For life insurance cases the standard tolerance test, with its fixed criteria probably remains the method of choice. In all other cases the Exton-Rose test is sufficient. In the very few cases where the diagnosis cannot be made on this test alone we may have to supplement it by the standard test and probably thereby overcome the difficulties in some cases. However, by mainly using the Exton-Rose



test we generally can save both the patient and the laboratory staff much time and work, while at the same time we obtain diagnostic data of about the same value as those obtained by the far more troublesome standard test.

### Summary.

The Exton-Rose tolerance test has been used in the Out-Patients Department of the Kommunehospital during 3 years for the diagnosis of diabetes mellitus. Owing to its short duration (1 hour) and the few laboratory analyses required (3 blood sugar estimations and 2 urine sugar estimations) this test offers advantages to both patient and laboratory staff. At the same time the test provided satisfactory data for the 54 cases investigated.

Patients with a blood sugar of less than 160 mg% at the third estimation should be regarded as non-diabetic. In patients with diabetes mellitus the fasting blood sugar is high and the third blood sugar estimation is more than 180 mg%, or the rise from the first to the second estimation exceeds 75 mg%. In the »uncertain range» the third blood sugar level lies between 160 and 180 mg%.

### References.

1. Allen, F. M.: »Glycosuria and diabetes». Boston, 1913, p. 1179. — 2. Exton, W. G. and A. R. Rose: Amer. J. Clin. Path., 4, 381, 1934. — 3. Exton, W. G. and A. R. Rose: Proc. Amer. Life Insur. Med. Dir. 18, 252, 1931. — 4. Goldberg, L. and R. Luft: Acta Medica Scandinavica, 132, 201, 1949. — 5. Hammar, L. and I. Hirschman: Johns Hopkins Hosp. Bull., 30, 306, 1919. — 6. Matthews, M. W., T. B. Magath and J. Berkson: J. A. M.A. 113, 1531, 1939. — 7. Schmidt, V. and A. Christensen: Ugeskr. Læg., 108, 315, 1946. — 8. Staub, H.: Biochem. Z., 118, 93, 1921. — 9. White, P. in E. P. Joslin et al.: »Treatment of Diabetes Mellitus», 1946, pp. 769—784.
-

Table I.

*Normal Tolerance According to the Exton-Rose Test (14 Non-Diabetic Patients).*

Case numbers	Sex and Age	Blood samples (mg%)			Urine samples (sugar concentration)	
		1	2	3	1	2
1 .....	F. 56	108	143	150	—	—
2 .....	F. 54	95	148	124	—	—
3 .....	F. 57	88	138	90	—	—
4 .....	M. 56	70	103	143	—	—
5 .....	M. 69	92	131	124	—	—
6 .....	M. 7	95	115	111	—	—
7 .....	F. 24	83	129	111	—	—
8 .....	F. 12	95	138	134	—	—
9 .....	F. 22	73	126	71	—	—
10 .....	F. 27	71	97	134	—	—
11 .....	F. 25	74	113	106	—	—
12 .....	M. 41 a)	76	138	138	—	—
	b)	72	129	125	—	—
13 .....	F. 35	71	119	105	—	—
14 .....	M. 42	90	95	88	—	—

Table II.

*Exton-Rose Tolerance Test Revealing Benign Glycosuria.*

Case numbers	Sex and Age	Blood samples (glucose in mg%)			Urine samples (sugar concentration)	
		1	2	3	1	2
1 .....	F. 14	82	131	124	+	+
2 .....	F. 65	109	119	128	(+)	+
3 .....	M. 46	79	127	117	—	+
4 .....	F. 33	81	124	124	—	+
5 .....	M. 52	52	124	159	—	+
6 .....	M. 76	123	160	146	—	+

Table III.

*Exton-Rose Tolerance Test on Pregnant Women with Glycosuria.*

Case numbers	Age in years	Months of pregnancy	Blood sugar (glucose in mg%)			Urine samples (sugar concentration)	
			1	2	3	1	2
1 .....	20	6	76	131	120	—	—
2 .....	18	7	97	185	181	—	(+)
3 .....	35	2	106	110	102	—	—
4 .....	34	2½	84	170	184	—	+
5 .....	25	7	61	120	106	—	—

Table IV.

*Exton-Rose Tolerance Test on Diabetic Patients with Normal Fasting Blood Sugar.*

Case numbers	Sex and Age	Blood sugar (glucose mg%)			Urine samples (sugar in concentration)		Other conditions present
		1	2	3	1	2	
1 .....	F. 61	95	252	283	—	++	obesity, hypertension
2 .....	M. 59	110	213	243	—	+	obesity, hypertension
3 .....	F. 67	127	217	271	—	+	
4 .....	M. 55	124	209	194	—	+	obesity
5 .....	M. 67	120	221	286	—	+	obesity
6 .....	M. 54	92	155	241	—	+	obesity
7 .....	M. 44	124	204	213	—	+	
8 .....	F. 64	117	222	251	—	+	hypertension
9 .....	F. 44	104	150	236	—	+	obesity
10 .....	F. 66	129	237	313	—	+	obesity
11 .....	F. 58	106	213	272	—	+	hypertension
12 .....	M. 65	101	176	270	—	+	obesity, boils
13 .....	M. 50	70	236	215	—	+	obesity
14 .....	M. 64	101	141	226	—	+	obesity, chronic alco- holism
15 .....	F. 71	117	183	240	—	+	obesity, hypertension
16 .....	M. 50	113	190	240	—	+	obesity, hypertension
17 .....	F. 52	104	170	277	—	+	gastric ulcer

Table V.

*Exton-Rose Tests in Patients with Definite Diabetes Mellitus.*

Case numbers	Sex and Age	Blood sugar (glucose in mg%)			Urine samples (sugar concentration)	
		1	2	3	1	2
1 .....	M. 73	195	314	385	+	++
2 .....	M. 68	200	321	355	—	+
3 .....	F. 73	216	275	338	—	+
4 .....	M. 58	191	204	294	+	++
5 .....	M. 66	177	219	314	+	+
6 .....	F. 55	149	189	214	—	+
7 .....	F. 66	329	336	385	+	++
8 .....	F. 47	141	202	241	—	+

Table VI.

*Exton-Rose Tolerance Tests on Diabetic Patients with »Uncertain Diagnosis».*

Case numbers	Sex and Age	Blood sugar (glucose in mg%)			Urine sugar		
		1	2	3	1	2	
1 .....	F. 75	114	167	156	—	+	obesity, hypertension
2 .....	F. 22	84	177	159	—	(+)	obesity
3 .....	M. 60	105	183	180	—	—	hypertension
4 .....	M. 61	134	195	186	—	—	obesity, chronic pyelo- nephritis

From the Laboratory of Pathology (Senior Physician: Prof. Dr. J. J. Th. Vos), and  
from the Medical Clinic, University of Groningen (The Netherlands).  
(Senior Physician: Prof. Dr. F. S. P. van Buchem.)

## Blood Disease and the So-Called Generalised Non-Reactive Tuberculosis.

(Typhobacillosis of Landouzy, Sepsis Tuberculosa Acutissima.)

By

A. ARENDS, Dr.

(Submitted for publication August 4, 1949.)

It is the purpose of this publication to draw attention to a form of tuberculosis, which although fortunately rare, is of interest on account of its unusual course, and which has been named variously by different authors. The severe changes in the blood picture, almost never absent, invite a closer consideration of the relationship between blood diseases and tuberculosis in general.

*Case I.* A man aged 47 years had been unsuccessfully treated for anemia by his doctor for six months. In hospital important changes in the blood picture were found (see accompanying chart). Initially this was believed to be a 'panmyelophthisis' as evidenced by the refractory anemia, the marked leucopenia, thrombocytopenia and the hemorrhagic diathesis. Later, when a considerable number of myeloblasts were found in the bone marrow obtained on sternal puncture, it was thought that this might be a case of acute aleucemic leucemia. It was not possible however to make a diagnosis with any degree of certainty.

The originally normal temperature was succeeded about two months before death by high fever, at first remitting in type, later continuous and finally intermittent. The patient suffered from rigors and became slightly jaundiced — in short, there developed the typical picture of widespread sepsis. Spleen and liver were however not palpable, and no lymph gland enlargement was found. Blood cultures made on various occasions were all sterile.

At autopsy the lower lobe of the left lung was found to contain a partly caseous, partly calcified lesion, about the size of a marble, while there were several enlarged and also partly caseous hilar glands. The enlarged spleen, 390 g, contained many round or irregularly shaped light-coloured foci (fig. 1). The liver was not enlarged, and on the surface were scattered fibrinous threads. There were no further abnormalities seen, the kidneys were apparently normal, and the bone marrow was soft and somewhat hyperplastic.

On *microscopic examination* the spleen showed numerous large and small, sometimes granular, sometimes homogeneous, necrotic foci, with marked hemorrhagic and fibrin-

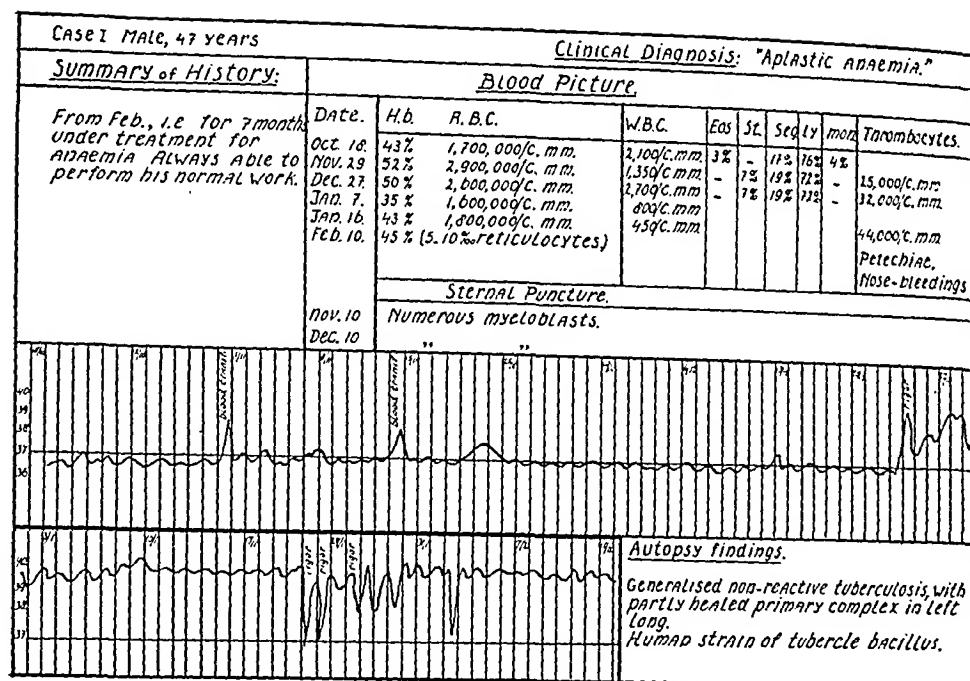


Chart 1.

ous exudate. In the surrounding tissues there was either absolutely no reaction evident, or at the most only a few lymphocytes. The splenic pulp was very vascular and oedematous (fig. 2).

The hilar glands were completely necrotic although their original tissue structure could still be recognised in places. Tuberculous granulation tissue was completely absent. The liver also contained many necrotic foci of varying size, rich in blood and fibrin, although these foci were generally noticeably less granular than those in the spleen. The lungs showed, besides an old calcified and fibrotic tuberculous focus, several necrotic areas with a slight superficial resemblance to tuberculous lesions.

The bone marrow, moderately rich in cells, contained small necrotic areas and small hemorrhages (fig. 3).

In all the foci tubercle bacilli were found without difficulty. By culture and animal inoculation the causative organism was found to be *M. tuberculosis* human type.

There was no evidence whatsoever to support the clinical diagnosis of acute leucemia: the liver, spleen and lymph glands were free from leucemic deposits. The blood picture must therefore be given the very unsatisfactory name of 'aplastic anemia'.

*Case II.* This was a 45-year-old man, who had been treated for an inflammatory process in the abdominal wall several months before admission to hospital. This lesion had healed well, but after the patient had been afebrile for some weeks the temperature rose again.

Important blood changes were found (see chart). The severe anemia, the continually increasing granulocytopenia and the fall in the thrombocyte count, together with the poor degree of cellularity of the bone marrow, led to the diagnosis of 'panmyelophthisis'.

The clinical picture of sepsis which the patient showed on admission to hospital, could either be considered as the cause of, or as the result of the panmyelophthisis. Blood culture was repeatedly negative. The spleen, originally palpable, became smaller during the course of the illness. Jaundice developed as a terminal feature.

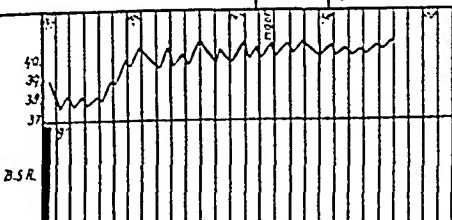
CASE II MALE, 45 YEARS				Clinical Diagnosis: "Aplastic Anaemia."						
Summary of History:		Blood Picture								
ILL for several months. First complaint was infection of Abdominal wall; treated successfully with protosil. Temperature became normal initially, but prior to admission to hospital a further rise in temperature.	Date.	H.b.	RBC.	Eos	St	Seg	L	WBC.	Thrombocytes.	
	July 7	64%	2,400,000/cmm	-	6%	12%	72%	1,500/cmm	54,000/cmm.	
	July 19	64%	2,400,000/cmm.					1,300/cmm		
	July 22	57%	3,000,000/cmm.					2,700/cmm		
	July 27	67%	3,000,000/cmm. (5% reticulocytes).	1%	12%	25%	57%	1,900/cmm 300/cmm	17,000/cmm. Haemorrhagic diathesis.	
		Sternal Puncture.								
		Reduced number of cells in bone marrow. Increased number of reticulum cells. No pathological cells.								
		Autopsy findings.								
		Generalised non-reactive tuberculosis. No old tuberculous foci.								

Chart 2.

The patient died after having been in hospital for  $3\frac{1}{2}$  weeks. At autopsy numerous yellow foci up to 3 mm in diameter were found in the spleen (295 g), liver (2,600 g) (fig. 4), and several enlarged glands in the porta hepatis. The bone marrow was vascular, but not hyperplastic. The other organs showed no further abnormalities.

It was seen on microscopic examination that the foci in the liver (fig. 5), spleen and lymph glands consisted of very vascular, partly granular, necrotic material, with very little or no surrounding tissue reaction. Only occasional giant-cells of Langhans were seen in the liver or lymph glands. Epithelioid cells and fibrous tissue formation were totally absent. The glands also showed a so-called large-cell hyperplasia. The bone marrow, relatively rich in cells, was the seat of small areas of necrosis and small hemorrhages. In the necrotic foci large numbers of tubercle bacilli could be found without difficulty (fig. 6). No old tuberculous lesions were found anywhere.

In this case too, a diagnosis of aplastic anemia was made, based on the blood changes observed.

**Case III.** A woman, 53 years of age, who had been ill for ten weeks prior to admission to hospital and who had had, amongst other complaints, various signs of a hemorrhagic diathesis, was found on examination in hospital to have a markedly abnormal blood picture (see chart). From the fact that there was a leucopenia present, with 20 % myeloblasts, this was initially considered to be a case of aleucemic leucemia.

The white cell count fell to 1,500 per cmm and it was noted with some surprise that myeloblasts could be found only with considerable difficulty in the later blood films, whereupon the diagnosis of leucemia began to be doubted.

After being ill for approximately four months the patient died, following the development of angina and oedema of the glottis which necessitated tracheotomy. The temperature, at first fluctuating round  $38^{\circ}\text{C}$ , rose in the last week to be replaced by an intermitting fever,  $38^{\circ}$ — $39.5^{\circ}\text{C}$ .

At autopsy the enlarged spleen (330 g) and liver (2,355 g) were seen to contain fairly numerous yellow nodules up to 3 mm in diameter. The pulmonary apices showed old tuberculous changes and there was inflammation of the peritonsillar tissues with oedema of the glottis.

Microscopic examination of the foci in liver and spleen showed them to consist of nec-

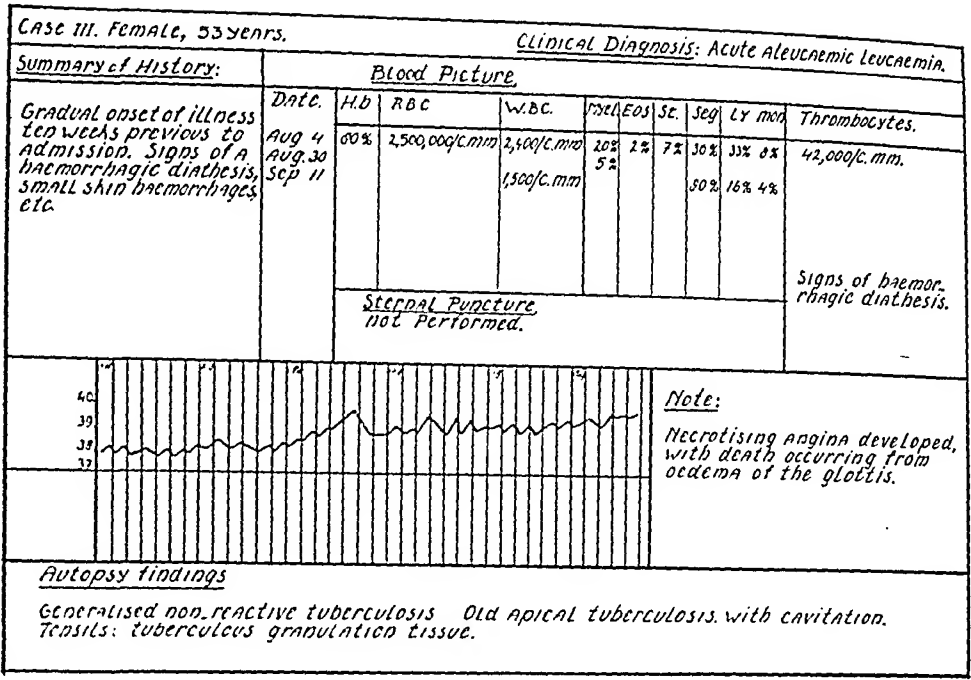


Chart 3.

rotic material, with appreciable nuclear degeneration and absence of any specific structure. The foci in the spleen were examined for tubercle bacilli: these were easily demonstrated. Guinea pig inoculation with material from the liver, spleen and an area of the left pulmonary apex yielded positive results. The tonsils also showed tuberculous changes. It was remarkable that in these alone was there any evidence of tuberculous granulation tissue round the necrotic foci caused by the tubercle bacilli. Leucemic deposits were present in liver and spleen. The bone marrow was very cellular and showed here and there areas with a fairly uniform cell structure (? myeloblasts). The findings in the splenic pulp, with its poor cell content, did not completely fit the picture of a leucemia.

Although it is difficult in this case to differentiate between an acute leucemia and a myeloid reaction, we are of the opinion that this must be a case of aleucemic leucemia, especially on the grounds of the clinical findings.

*Terminology:* Typhobacillosis of Landouzy; Sepsis tuberculosa acutissima; non-reactive tuberculosis.

The form of tuberculosis described here may be found referred to in the literature under the name of Typhobacillosis of Landouzy. This name was used by Landouzy to indicate a syndrome, the cause of which was a 'toxemic' form of tuberculosis, with a clinical picture resembling typhoid fever in many respects.

It is very questionable whether the form of tuberculosis described in the present article is identical to typhobacillosis. The autopsy reports in Landouzy's articles are very short, and nowhere does he definitely state that necrotic tuberculous foci were found in the internal organs. One obtains more the impression that he is dealing with a generalised, and severe reaction to a localised tuberculous process, accompanied by high fever. The fact, also, that according to

Landouzy, a certain proportion of patients suffering from typhobacillosis recovered, raises the question of whether identical conditions are being considered. Recovery can hardly be expected from the form of tuberculosis described in this paper.

Scola introduced a different term in 1918. As he believed he was dealing with an extremely acute type of miliary tuberculosis he conceived the name 'sepsis tuberculosa acutissima'. Harbitz was one of several authors to use the term 'tuberculous septicemia'. This name cannot be substantiated by the fact that in this disease tubercle bacilli may be repeatedly cultured from the blood. There are no reports of such cases in the literature. One is not led to look for tubercle bacilli since the clinical picture bears not the slightest resemblance to tuberculosis (see later).

One argument against the suggestion that this is a true tuberculous septicemia lies in the fact that this condition far from constantly runs a more acute course than miliary tuberculosis. Case II serves as an example of this, where the signs and symptoms had been present for at least fifteen weeks.

In view of the longer duration of the process Rennen (1922) considered the name 'sepsis tuberculosa gravissima' to be more appropriate, thus maintaining however the idea of a septicemia.

Siegmund (1929) introduced a completely different, and at the same time more fitting name. He used the term 'generalised non-reactive tuberculosis' indicating thereby that one found necrotic tuberculous foci in many organs, but without the presence of tuberculous granulation tissue.

### Pathology.

The necrotic areas are unsharply defined and are continuous, without any line of demarcation, with the normal tissues. Occasionally they are surrounded by a narrow zone of lymphocytes. Epithelioid cells, giant-cells of Langhans, fibroblasts and formation of connective tissue are generally totally absent. The necrotic material is very unlike tuberculous caseous material in appearance. It lacks the homogeneous character of this latter, and often appears granular or streaky due to the presence of disintegrated pyknotic nuclei and fibrinous exudate. The original structure may sometimes still be recognisable after special staining (Matisseck). Very occasionally there is a superficial resemblance between these foci and small abscesses (Lederer). One of the most striking features is the absence of tuberculous granulation tissue: in fact the appearance of the lesions scarcely suggests a diagnosis of tuberculosis, until it is seen in Ziehl-Neelsen preparations that the foci are packed with tubercle bacilli. This is one of the special features of the non-reactive tuberculosis.

Rarely one finds a reactive process at the edge of a focus, suggesting the tuberculous nature, although it may not do so very strongly (Holzer, Friedemann, Hegler, von Wijsz, Matisseck and others).

The density of the dissemination of the foci is liable to considerable variation,



not only in different cases, but also in any particular case can it vary from organ to organ. The largest number of foci are generally found in the liver and spleen. In connection with this it may be noted that the term 'primary tuberculosis of the reticulo-epithelial system' is also applied (Friedemann), since in most instances the lymph glands and probably also the bone marrow are affected as well.

Other organs, such as kidneys and lungs are less seriously affected: the kidneys, for example, are found to be completely free from lesions in about half the cases. Theoretically lesions are to be expected in every organ, and most striking is the fact that tuberculous meningitis does not occur. Another special characteristic has been believed to be the absence of old tuberculous foci in the body, and this has led to the theory that there exists thus a form of tuberculosis which develops in older individuals who have never been infected with the tubercle bacillus (Loeschke, Pagel, Siegmund, Dugge, Velten and Fatum). The body would therefore be completely deficient in any immunity to the infection. The negative result of the tuberculin test, performed in only a small number of the cases, also points in this direction. If one examines the cases described in the literature then it is found that old tuberculous lesions are sometimes found: Nasse — old calcified pulmonary foci, Harbitz — calcified hilar glands, Balint and Roth — old healed tuberculosis of the pulmonary apices, Krasso and Nothnagel — caseous encapsulated axillary glands, von Wijsz — two cases with almost inactive chronic pulmonary tuberculosis. Two of the cases described here show old tuberculous changes, case III an old cavernous pulmonary tuberculosis, and case I partially healed primary complex. In case II there was also a weakly positive Pirquet reaction.

The suggestion that the non-reactive course of this form of tuberculosis may be explained as being due to a primary infection with tubercle bacilli in older individuals cannot be upheld in our opinion and is certainly not applicable in all cases.

### Type of Tubercle Bacillus.

It has long been maintained, especially as an outcome of the investigations of Löwenstein, that the causative organism in non-reactive tuberculosis is the avian tubercle bacillus (Nasse, Krasso and Nothnagel, Lederer, Dugge). There is no certain indication, however, that this is the case. On the contrary, many instances are cited in the modern literature where it was shown with certainty that human tubercle bacilli were present (Rennen, Jacobowicz, Velten and Fatum, Siegmund). In the one case in the present series in which the type of tubercle bacillus was determined we found *M. tuberculosis* human type (Case I). It is remarkable that in the Anglo-saxon literature the opinion is still held under the influence of older observations, that these cases are due to infection with the avian type of tubercle bacillus (Crail).

A more satisfactory explanation of the pathogenesis is obtained in our opinion by a closer examination of the clinical features of this condition.

### Clinical Features.

Generally the patient is obviously very ill, with the high temperature dominating the picture, while investigation of the internal organs brings to light practically no abnormalities.

The fever is often continuous in type, but may on occasion be remittent or intermittent. Other constant features are: severe malaise, early development of exhaustion and enlargement of the spleen. The disease often commences acutely sometimes even accompanied by rigors; less frequently do the signs and symptoms make their appearance gradually. For this reason the actual duration of the illness may be difficult to determine. Even when there is apparently an acute onset it often becomes manifest by careful questioning of the patient that various vague complaints had existed previously.

Of particular interest are the striking changes in the blood picture, seen in a very large percentage of cases. A simple leucocytosis is practically never found. The majority of cases show an increasing leucopenia in which there is principally a decrease in the granulocyte count (Holzer, Friedemann, Roth, Hegler, Siegmund). All stages of transition are found between severe leucopenia and agranulocytosis (Scholz, Nasse, Harbitz, Hegler, Steinbrink, Siegmund, Matisseck, von Wijsz). Changes in the blood picture are described, similar to those of acute leucemia, while other investigators speak of a myeloid reaction (Reiche, Eckel, Wätjen, Siegmund, Leibowitz). Similarly, the red cell picture in many cases is abnormal, mainly in the direction of an anemia. The blood changes are often so marked and dominate the clinical picture to such an extent, that one is naturally led to consider the existence of a disease of the blood, with sepsis as a terminal complication.

Thus, one may find a blood picture resembling that of agranulocytosis, aplastic anemia or acute leucemia, and all the clinical features of these conditions may be present — hemorrhagic diathesis, skin changes, necrotising inflammatory lesions of the mucous membranes of the mouth and throat. Other diseases of the blood may be co-existent: a combination of this form of tuberculosis with chronic myeloid leucemia has been repeatedly described (Krasso and Nothnagel, Fischer, Gosau, Matisseck, von Wijsz), and even an occasional case has been reported in which there was a combination with polycythemia (Rennen, Lederer).

These blood changes help to give a better insight into the true nature of this type of tuberculosis. The following case serves as a further example.

*Case IV.* A 54-year-old woman was admitted to the Medical Department on 17. 5. 47. According to her own doctor she had become ill fourteen days previously with signs of a pneumonia. She was given 20 g of sulphadiazine spread over several days. At the same time she developed a festering thumb and the right calf became swollen. These had both resolved by the time the patient was admitted to hospital, but the temperature had remained elevated.

Condition on admission: A very ill, febrile woman (temp. 40.3° C). Moderately severe follicular angina present. Heart and lungs showed no abnormalities. Liver and spleen not palpable.

X-ray of chest: Nil abnormal seen.

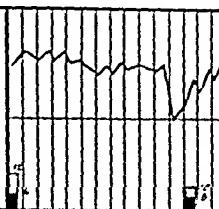
CASE II Female, 59 years.		Clinical Diagnosis: AGRANULOCYTOSIS Sulphadiazine?							
Summary of History:		Blood Picture							
Two weeks previously had become acutely ill, diagnosis of pneumonia. Treated with sulphadiazine, 20 gm., after which the temperature did not return to normal. For this reason admitted to hospital.		Date.	H.b	R.B.C.	W.B.C.	Eos	St	Seg	Ly, mono.
		MAY 17	71%	4,100,000/cmm	200/cmm	-	5%	25%	70%
		MAY 18			900/cmm	-	5%	25%	60%
		MAY 21			1,000/cmm	-			10%
		MAY 22			1,500/cmm	-			
		MAY 24			2,500/cmm	-	16%	56%	24%
		MAY 26			4,600/cmm	-	17%	69%	10%
		MAY 27			5,300/cmm	-	16%	54%	17%
		MAY 31			6,700/cmm	-			
		Sternal Puncture:							
		No bone marrow obtained.							
		Treatment:							
		Penicillin, 300,000 units daily. Blood transfusions. Pentnucleotide and pyridoxine.							
		Note:							
		On admission there was also present follicular tonsillitis which healed during the period in hospital.							
Autopsy findings:									
Dissemination of									
Very extensive non-reactive tuberculous foci. (This was only discovered on microscopic examination.) Old tuberculosis of hilar lymph glands.									

Chart 4.

Blood picture: Hemoglobin: 71 %, R. B. C.: 4,100,000/cmm, W. B. C.: 200/cmm, Differential count: Stab cells: 5 %, segmented polymorphs: 23 %, lymphocytes: 70 %.

Sternal Puncture: no bone marrow obtained.

Blood Culture: no growth.

A diagnosis of agranulocytosis was made, possibly due to the preceding sulphadiazine therapy. The patient was given the usual treatment, penicillin, 300,000 units daily, blood transfusions and also pentnucleotide and pyridoxine.

Progress: In spite of the fact that the agranulocytosis disappeared completely (see chart), the woman remained obviously ill and the fever did not subside. The angina resolved. Death occurred on 1. 6. 47.

*Autopsy findings:* Enlarged and partly caseous hilar glands, and caseation of the paratracheal glands. In the upper lobe of the right lung was a small yellowish caseous area. Spleen enlarged (365 g), with slight oedema of the pulp.

Only on microscopic examination was it found that there were widely disseminated necrotic areas in spleen, liver, kidneys and bone marrow, in which numerous tubercle bacilli could be demonstrated in Ziehl-Neelsen preparations. The edges of these foci showed no characteristic granulation tissue, but only occasional epithelioid cells and giant-cells of Langhans.

One of the paratracheal lymph glands was the seat of an old caseous tuberculous focus, encapsulated by fibrous tissue, and with a few epithelioid cells in the surrounding tissues.

The lungs showed no evidence of tuberculosis, and were likewise free from signs of pneumonia.

The bone marrow appeared active in so far as it contained numerous cells.

### Relationship between the Tuberculous Infection and the Agranulocytosis.

In this case there was present an agranulocytosis, presumably attributable to the sulphadiazine given before admission to hospital. By means of modern thera-

peutic measures the agranulocytosis was overcome, but the temperature remained elevated, and at the time of death there were still signs of sepsis.

An explanation was only obtained on histological examination of the various organs. There was a generalised tuberculosis which had given rise to widespread necrotic foci, but without any local tissue reaction. The large number of tubercle bacilli in these foci makes the tuberculous etiology more than self-evident.

We would like to stress the fact that, as in this case, it is repeatedly observed in this type of tuberculosis the focal lesions are not discovered on macroscopic examination, but only when tissue sections are examined. At autopsy one finds no marked changes apart from degeneration and hyperemia of the internal organs (Scholz, Harbitz, Siegmund). It is for this reason that the case reported here is of so great interest, since, in our opinion, it gives a very clear indication of the pathogenesis of the form of tuberculosis in question.

It is similarly desirable to make a comparison with other inflammatory processes occurring in the presence of agranulocytosis. Simple infecting organisms may, as is well known, in the absence of an adequate leucocyte response, give rise to necrosis unaccompanied by normal inflammatory reaction. It is conceivable thus that the absence of any reaction (lack of tuberculous granulation tissue formation) may be an important factor in this type of tuberculosis.

### Pathogenesis.

The opinion has fairly generally been held that the changes in the blood picture, leucopenia, agranulocytosis, panmyelophthisis, myeloid reaction, are the result of the severe, acute haematogenous spread of the tuberculosis, whereby the preference shown by the tubercle bacilli to localise in the reticulo-endothelial tissues (see above) may be a causal factor of some importance (Siegmund).

There is much evidence in our opinion in favour of the converse interpretation, *i. e.* to consider the non-reactive tuberculosis as a result of a constitutional or an acquired insufficiency of the hemopoietic system. In other words, the disease of the blood forming organs already in existence will be associated with such a serious lack in power of resistance that the tuberculous infection is allowed to proceed unhindered, with the development of the picture of non-reactive tuberculosis (von Wijsz, Matisseck). Having reached this conclusion one is led automatically to the next stage, namely to seek the cause, as Matisseck did, in a failure of the leucocyte (polymorphonuclear) defence mechanism.

All the blood diseases mentioned (leucemia, agranulocytosis, and panmyelophthisis) have in common an inadequate leucocyte system. If this supposition is correct, the question arises of whether the polymorphonuclear cells are not of greater importance in the defence of the body against tuberculous infections than is generally believed at present. Although the problem of the function of the polymorph leucocyte in tuberculosis is not yet unanimously solved, a certain amount of evidence has been derived from animal experiments that is of importance. Particular reference has been made to this by Matisseck.

Exudates rich in polymorph cells, with phagocytosis of bacilli, have been observed by many investigators (Gardner, Medlar, Sherwood, Long and Vorwald) in the early stages of experimentally induced tuberculosis, and this has been considered to be an essential feature of the process. Chemotactic influence of the tubercle bacillus on polymorph leucocytes has also been described (Cutcheon and Dixon, Wartman and Ingraham, Doan, Sabin and Forkner).

The investigations of Woodruff are of especial importance. He demonstrated that tubercle bacilli are phagocytosed by polymorph leucocytes, which in their turn are phagocytosed by large mononuclear cells. By the action of the polymorphs the tubercle bacilli are, as it were, prepared for the further action of other cells with the result that the bacilli are rendered harmless.

Takeuchi has inoculated animals with tuberculosis after causing leucopenia by the administration of benzol. It was found that these animals showed very little resistance and died rapidly. Histologically he found sero-hemorrhagic inflammatory reactions.

### Conclusions.

The fourth case is particularly illustrative in that it may be likened to a natural experiment which confirms the theory expounded above concerning the origin of non-reactive tuberculosis.

Case I also merits further mention. This was a patient who had been under treatment for several months on account of a blood disease ('aplastic anemia'). During the period in hospital the temperature suddenly rose and remained elevated, presumably at the time at which the hematogenous dissemination of the tubercle bacilli occurred. The case thus illustrates the development of tuberculosis during the course of a blood disease of long standing.

In two cases described the question must remain open as to whether they must be classed as 'aplastic anemia' or 'acute leucemia'. Such cases are well known even in the absence of tuberculosis.

The opinion is held (among others by Henning), that 'aplastic anemia' and 'acute leucemia' may be considered to represent different phases of activity of the bone marrow in one and the same disease. We doubt strongly however whether such cases may be compared to those in which there is gross involvement of the myeloblasts from the beginning. The decision between 'aplastic anemia' or 'acute leucemia' is of no importance to the support or otherwise of our supposition, since in both instances there is constantly a leucocyte insufficiency.

Finally it may be mentioned that there is relatively extensive literature dealing with the myeloid reaction precipitated by tuberculosis and the simultaneous development of tuberculosis and aplastic anemia or panmyelophthisis (Roth, Jünger, Gudzent, Wieckmann, Polak Daniels, Geissler and Wurm, Stöger, Derman and Lifschitz, Karlmark and Olovson, and others). Examination of these cases shows that almost always a generalised tuberculosis was co-existent, characterised either by the formation of no tuberculous granulation tissue or by the

formation of only very little, without their being classified by the respective authors as non-reactive tuberculosis.

It is conceivable that many of these cases, in connection with the theory put forward above, are examples of non-reactive tuberculosis superimposed on an already existent bone marrow insufficiency.

### Summary.

Four cases are presented of a combination of different diseases of the blood and so-called non-reactive tuberculosis.

This form of tuberculosis is discussed in some detail, with reference to these cases and also to the literature, and the opinion is advanced that the abnormal picture presenting here is due to the pre-existence of a bone marrow defect.

The fourth case is particularly instructive in connection with this supposition.

### Literature.

Balint: Tuberkulöse Sepsis. Wiener Archiv. inn. Med. 10, 165, 1925. — Crail: Myelofibrosis, splenomegaly and megakaryocytic myelosis. Arch. Int. Med. 78, 14, 1946. — Cutcheon and Dixon: Chemotropic reactions of polymorphonuclear leukocytes to various micro-organisms. Arch. p. Path. 21, 749, 1936. — Derman and Lifschitz: Zur Frage der kombinierten Erkrankung an atypischer aplastischer Anämie und subakute Miliartuberkulose. Z.bl. f. Path. 49, 129, 1930. — Dugge: Ueber einen Fall von »Sepsis tuberculosa gravissima« (Geflügeltuberkulose?). Beitr. Klin. Tbk. 71, 538, 1929. — Eckel: Ein Fall von Typhobacilliose Landouzy unter dem Bilde der aleukämischen Mikromyeloblasten Leukämie. Med. Klin. 223, 1929 I. — Fischer: Über einen eigenartigen Fall schwerster Tuberkuloseinfektion. Beitr. Klin. Tbk. 60, 86, 1924. — Fischer: Miliartuberkulose und Leukämie. Beitr. Klin. Tbk. 87, 335, 1936. — Friedemann: Ein Fall von nekrotisierender Tuberkulose des Reticuloendothelialsystems mit sekundärer Miliartuberkulose. Arch. f. Verdauungskrankheiten 37, 167, 1926. — Gardner: The cellular reactions to primary infection and reinfection with the tubercle bacillus. Amer. Rev. of Tuberc. 22, 379, 1930. — Geissler and Wurm: Tuberkulose und myoblastische Reaktion (Ein Beitrag zur Pathologie der tuberkulösen Erstinfektion des Erwachsenen). Klin. W.schr. 1212—1214, 1939 II. — Gosau: Chronische myeloische Leukämie mit Sepsis tuberculosa acutissima. Fol. Haemat. 52, 271, 1934. — Gudzent: Bericht über einen unklaren Krankheitsfall (Tuberkulose, myeloische Leukämie). Dtsch. med. W.schr. 12, 475, 1922. — Harbitz: Acute atypical miliary tuberculosis. Acta tuberc. Scand. 10, 59, 1931. — Harbitz: »Atypical« tuberculosis and especially tuberculosis in the blood-forming organs and tubercle bacillary septicaemia (from a pathological standpoint). Acta tuberc. Scand. 5, 1, 1931. — Hegler: Zur Klinik der Typhotuberkulose (»Typhobacilliose« Landouzy, »Sepsis tuberculosa acutissima« Scholz). Dtsch. Arch. klin. Med. 183, 1, 1938. — Henning: Beobachtungen zur Pathogenese der akuten Myeloblasten Leukaemie. Dtsch. Arch. klin. Med. 178, 538, 1936. — Holzer: »Das Krankheitsbild der Typhobacilliose« Beitr. Klin. Tbk. 66, 245, 1927. — Jacobowicz: Sepsis tuberc. acutissima. Beitrag zum Virulenzproblem der Tuberkelbacillen. Beitr. z. Klin. d. Tbk. 85, 247, 1934. — Jünger: Ein Fall von Leukaemie, kompliziert mit Miliartuberkulose. — Karlmark and Olovson: Über gleichzeitiges Vorkommen von Tuberkulose und Anaemia perniciosa Biermeri. Beitr. z. Klin. d. Tbk. 79, 772, 1932. — Krasso and Nothnagel: Atypische Tuberkulose (Geflügeltuberkulose) bei myolischer Leukämie. Wien. Arch. inn. Med. 11, 507, 1925. — Lederer: Über Geflügeltuber-

kulose des Menschen mit Polyzythämie. Wien. Arch. inn. Medi. 3, 23, 1923. — Leibowitz: Tuberculous sepsis with a myeloblastic blood picture. Arch. of Path. 25, 365, 1938. — Loeschke: Die hämatogenen Tuberkulosen (Pathol. anat. Referat). Beitr. z. Klin. d. Tbk. 81, 171, 1932. — Long and Vorwald: The cellular reaction to infection with tubercle bacilli. Experiments on the cornea in animals of varying susceptibility. Amer. Journ. of Pathol. 7, 555, 1931. — Loewenstein: Das Krankheitsbild der Hühnertuberkulose beim Menschen. Med. Klin. 46, 1782, 1928. — Loewenstein: Beitrag zur Leistungsfähigkeit der direkten Züchtung der Tuberkelbazillen aus dem infektiösen Material mit einem Beitrag zur Geflügeltuberkulose beim Menschen. Wien. Klin. W.schr. 35, 808, 1931. — Loewenstein: Über 3 Fälle von Hühnertuberkulose beim Menschen. — Matisseck: Über die Bedeutung von Knochenmarkschäden für den areaktiven Verlauf generalisierter Tuberculose. Virch. Archiv 308, 783, 1943. — Nasse: Ein weiterer Fall von Sepsis tuberculosa acutissima, vermutlich Geflügeltuberkulose. Z.bl. Path. 53, 209, 1931. — Pagel: Pathologische Anatomie der hämatogenen Streuungstuberkulose. — Polak Daniels: Over afwykingen in het bloed by een lyder aan subacute miliair tuberculose. Ned. Maandschr. v. Gen. 375, 1922. — Reiche: Pathologisch-Anatomische Untersuchungen über die Tuberkulose des Knochensystems. Julius Springer, Berlin 1932. — Rennen: Über Sepsis tuberculosa gravissima bei einem Fall von Polycythaemie. Beitr. z. Klin. d. Tbk. 53, 197, 1922. — Roth: Über die Tuberkulöse Sepsis. Beitr. z. Klin. d. Tbk. 71, 631, 1929. — Roth: Über einen bemerkenswerten Blutbefund bei einem Fall von subakuter Miliärtuberkulose. Ztschr. f. klin. Med. 78, 75, 1913. — Sabin, Doan and Forkner: Studies on Tuberculosis. Journ. of exper. med. 52, 1930. Suppl. 3. — Scholz: Die Formen der durch Tuberkelbazillen verursachten Sepsis (Typhobacillose Landouzy) und Miliärtuberkulose. Inaug. Diss. 1918. — Scholz: Die Formen der durch Tuberkelbazillen verursachten Sepsis tuberculosa acutissima und Miliärtuberkulose. Berl. klin. W.schr. 55, 1146, 1918. — Sherwood: Some cellular reactions and immunity in tuberculosis. Journ. of immun. 17, 481, 1929. — Siegmund: Areaktive generalisierte Tuberkulose. Beitr. z. Path. Anat. 103, 431, 1939. — Siegmund: Z.bl. inn. Med. 42, 879, 1936. — Steinbrinck: Über Sepsis tuberculosa acutissima mit Agranulocytose. Med. Welt. 12, 381, 1938. — Stöger: Myeloblastenreaktion bei atypischer Tuberkulose (Geflügeltuberkulose). Wien klin. Wochenschr. 21, 1940. — Takeuchi: Über die Histogenese der tuberkulösen Veränderungen. Transactions Societatis Pathol. Japonicae. 25, 1, 1936. — Velten and Fatum: Beitrag z. Sepsis tuberculosa acutissima. Beitr. z. Klin. d. Tbk. 94, 672, 1940. — Wartman and Ingraham: Chemotactic properties of tuberculophosphatide and tuberculopolysaccharide. Arch. of Pathol. 29, 773, 1940. — Wätjen: Sepsis tuberculosa gravissima bei klinisch gebesserter myeloischer Leukämie. Münch. Med. W.schr. 1551, 1935 II. — Wieckmann: Miliärtuberkulose und sekundäre Myeloblastose. Med. klin. 18, 1086, 1922. — Woodruff: A free growth period of tubercle bacilli in the guinea pig omentum as related to the hypersensitive state. Am. Journ. of Pathol. 10, 739, 1934. — Von Wysz: Die Tuberkulosepsis und die Typhobacillose Landouzy. Helvetica Med. Acta. 4, 430, 1940. Helvetica. Med. Acta 5—6, 683, 1940—41.

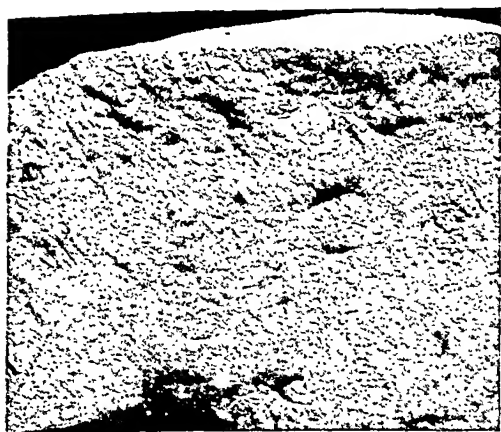


Fig. 1. *Spleen*: cut surface, showing widely disseminated round and irregularly shaped foci, fairly sharply demarcated and light in colour.



Fig. 2. *Spleen*: several irregularly shaped foci. Absence of tuberculous granulation tissue.

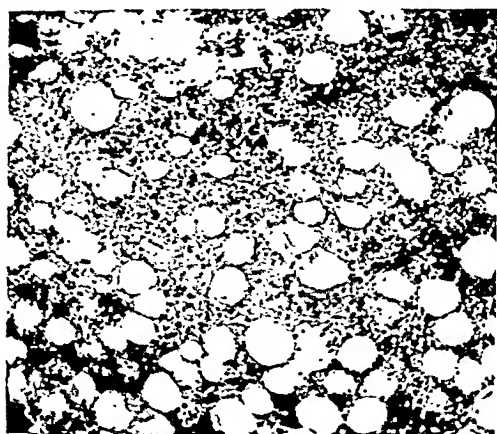


Fig. 3. *Bone Marrow*: moderately rich in cells and showing poorly demarcated light-coloured necrotic foci.

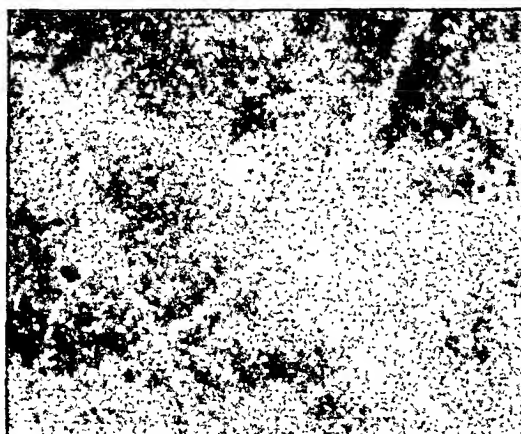


Fig. 4. *Liver*: detail of surface. Widely disseminated necrotic foci.

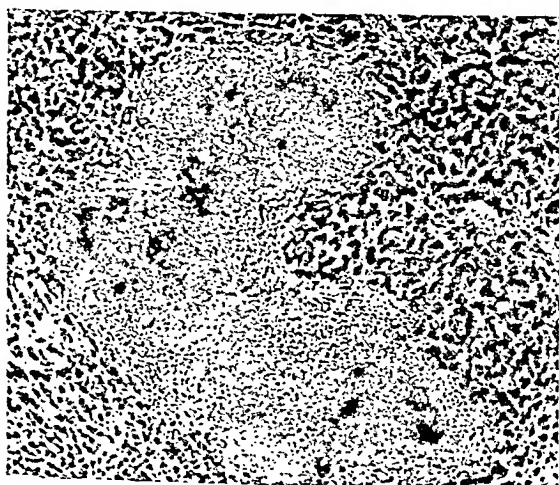


Fig. 5. *Liver*: necrotic focus. The granular appearance is due to the large number of nuclear remains.

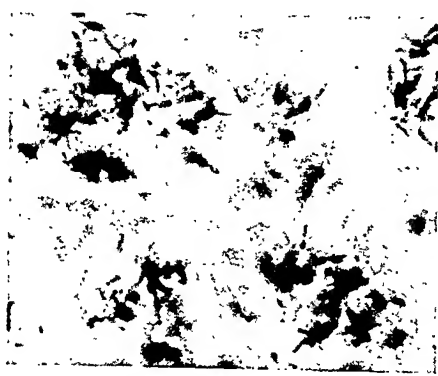


Fig. 6. *Liver*: Ziehl-Neelsen preparation. The foci contain numerous tubercle bacilli. (Oil immersion.)



From the Royal Pensions Board's Hospital, Nynäshamn, Sweden.  
(Chief: F. Sundelin, M. D.)

## Streptococcus Agglutination in Cases of Chronic Polyarthrititis.<sup>1</sup>

By

CARL CÖSTER.<sup>2</sup>

(Submitted for publication August 5, 1949.)

In 1931 Cecil, Nicholls and Stainsby (1) showed that sera from patients with *chronic polyarthrititis* (c. p.) agglutinated  $\alpha$ -streptococci to nearly 100 % while, on the other hand, sera from patients with *rheumatic fever* or other diseases, or from healthy persons, only gave positive reactions in a few cases. In American quarters a number of authors (2—9, 18) have subsequently been able to verify these statements on the whole.

Interest in this matter was very slight in Scandinavian quarters until recent years. Thus the first publication, by Packalén (10), appeared in 1943. Subsequently it was not until 1946 that Kalbak (11) carried out a comparative investigation into antistreptolysin titers and the capacity to agglutinate streptococci of sera from patients with *rheumatic fever* and c. p. Some Swedish investigations (12—15) were also published in 1946.

Cecil and co-workers (1) employed an  $\alpha$ -streptococcus, which they isolated from a patient with c. p. They considered that this bacterium was the cause of the disease and called it «*the typical strain*». In 62 % of their cases they were able to isolate this bacterium from the blood in cases with c. p.

The majority of other authors have worked with  $\beta$ -streptococci belonging to Group A. Streptococci from groups B, C, D, and E have also been tried but did not prove to give equally good results.

Dawson and co-workers (4) worked out a method which Packalén (10) employed. Kalbak (11, 24) made a slight modification of this method. Edström and Winblad (12) et al. (14, 15) followed Kalbak's method. With both these methods living bacteria are employed.

<sup>1</sup> The investigation carried out with the help of a contribution from King Gustavus V's 50th Birthday Fund.

<sup>2</sup> Hudiksvall (Sweden).

On the other hand, Cecil and de Gara (9) obtain the best results with dead bacteria and centrifugation of the serum antigen mixture. Thulin (13, 25) works with bacteria killed by means of autoclaving (120°, 2 hours) and considers that this does away with a capsule antigen which checks agglutination.

According to Winblad (16), the antigen which is employed in Dawson's and Kalbak's methods is a readily destructible surface antigen.

The majority of authors have been able to prove that sera from patients suffering from *rheumatic fever* gave positive agglutinations in only an inconsiderable number of cases. Edström and Winblad (12) described a couple of protracted cases in which positive agglutinations appeared 4 to 6 months after the onset of the illness. However, with his O-antigen Thulin (25) obtained positive agglutinations in 86.4 % of the 54 cases he examined 3 to 6 months after the onset.

In table 1 a collocation is made of the works of the majority of the above-mentioned authors. It is divided into three groups according to the antigen employed.

Group I comprises the investigations in which  $\alpha$ -streptococci constituted the antigen. The group is small, and the results are discrepant.

Table 1.

Antigen	Author	Lowest pos. titre	Chronic Polyarthritis		Controls % pos.	Rheum. fever % pos.
			No.	% pos.		
I $\alpha$ -streptococci	Cecil (1) .....	1 : 640	103	94	2	
	Gray and Gowen (2) .....	1 : 640	60	62		
	Nicholls (3) .....	1 : 160	613	45		
II $\beta$ -streptococci	Dawson (4) .....	1 : 160	152	69	2.4	
	Keefer (8) .....		22	55	2.2	26
	Dawson (6) .....	1 : 160	666	51	1.4	1.1
	Packalén (10) .....	1 : 160	17	59	11	37.5
	Cecil (9) .....	1 : 160	268	60	0	0
	Kalbak (24) .....	1 : 40 1 : 40	168 73	77 79		10
	Edström and Winblad (12)	1 : 40	50	76		25
	Olhagen (14) .....			54	10	
	Hedlund (15) .....		103	42		27
	Ragan and Tyson (18) ...		142	63		
III O-antigen	Thulin (25) .....	1 : 40	285	84.9	7.6	86.4



in arriving at a decision as to whether the disease is in a progressive, regressive or inactive stage. Further, for all the patients with rheumatic diseases the sedimentation rate was checked every week. In a number of cases the antistreptolysin titers were determined and as a rule showed normal values.

In 1947 Thulin and Berglund (17) were able to prove pos. agglutinations in a large number of cases with glomerulonephritis. This indicates that attention must be paid to this point in agglutination investigations in cases of c. p. Therefore cases in which there was any suspicion of nephritis were not included in the investigation.

Cases the treatment of which had already been begun were also excluded, for reasons which will be discussed later.

The chronic polyarthritis material was divided into three groups, one comprising active, progressive, moderately severe to severe cases, one comprising slight, and one inactive to healed cases of c. p.

The group »severe to moderately severe cases of c. p.» comprises patients with moderate to considerable subjective trouble, objective findings of capsular swelling, effusion, reduced motility, deviations and deformities in a number of joints, or strongly pronounced changes in a few. These cases had had moderate to severe changes as shown by X-ray and, as a rule, moderately raised or high sedimentation rates. Further, in a number of cases muscular atrophies and trophic disturbances in the skin with atrophy and increased secretion of sweat, especially in the hands and feet could be observed, and in many also changes resembling scleroderma in the hands. The patients were afebrile to subfebrile.

The group »slight cases of c. p.» comprises patients with slight subjective trouble, slight objective provable joint changes, such as capsular swelling, inconsiderable restriction of movement in a few joints, and less pronounced roentgenological findings. The patients had slightly to moderately raised sedimentation rates.

Finally, the group »inactive to healed cases of c. p.» comprises patients with moderate to inconsiderable subjective trouble, and with slight to considerable objective joint changes, but the latter were conditioned by »deformation changes» after the rheumatic joint processes. The sedimentation rate was normal to slightly raised.

The group »status post polyarthritidem acutam» consists of patients with inconsiderable to no provable joint changes. They were afebrile, had normal to slightly raised sedimentation rates, which as a rule became normal before the patients were discharged. One or two had cardiac changes of the mitralis vitium type and ecg. changes of the prolongation of the P—R interval type.

For inclusion in the group *spondylarthritis ankylopoetica*, the criteria were, in addition to the typical restriction in movement in the vertebral column, X-ray findings from the vertebral column or at least a sclerosis in the sacro-iliaca joints and a raised sedimentation rate.

For the control group the condition was laid down that there was no evidence of rheumatic affections, or present or recent streptococcic infection. The patients must also have normal sedimentation rates.

## Method.

Kalbak's method (11, 24) was followed for carrying out the agglutinations. The antigen used was a streptococcus belonging to Group A, type 1, which was courteously placed at my disposal by Kalbak. The antigen was prepared at the *Hygienic-Bacteriological Institution at Uppsala University* by B. Zetterberg. The further

investigation was carried out by the present author at the *Royal Pensions Board's Hospital at Nynäshamn*.

The condition for a reaction to be considered to be positive was that there should be flocculation in serum dilution 1:160. Further, a pre-condition was always flocculation of at least grade 2 according to Kalbak in the first tube. As the highest titre was indicated the serum dilution in which clear flocculation could still be clearly observed macroscopically. All the readings-off were made by the same investigator and under the same optical conditions. Double determinations were made on a large number of sera. The discrepancies proved to be small.

At each determination a serum which was known to be pos. and one which was known to be neg. were included as controls.

### Results and Discussion.

The control group included in the investigation consisted of 102 cases with 2 pos. agglutinations, i. e. 2 % pos., when the limit set for pos. reactions in this investigation was at a serum dilution of 1:160.

One of the pos. reactions was shown by a patient who had been nursed under the diagnosis *debilitas + psychoneurosis*, and who had had a sedimentation rate of 4 mm. The other case was nursed under the diagnosis *dorsal insufficiency*, had a sedimentation rate of 4 mm. and the X-ray examination of the lumbar vertebra and pelvis revealed normal conditions.

If the limit for pos. agglutinations had been set a titre of 1:80, the number of pos. cases would not have amounted to more than 3, i. e. 3 % pos., but the number of doubtful reactions, which is now 1, would then have risen to 9 (see table 2), which must be considered to afford good reason setting the lowest pos. titre at a serum dilution of 1:160.

The investigation included 224 cases with definite c. p., 130 of which, i. e. 58 %, gave pos. agglutinations. It appears from table 2, in which the results of the investigation are shown and the distribution of the cases over the different serum dilutions is indicated, that over half of all the pos. agglutinations are found with the serum dilution 1:160 and fully one-quarter with the 1:320 dilution.

The 224 cases of c. p. are distributed over the various groups so that 132 fall into the »severe—moderately severe», with 80 % pos., 75 into the »slight», with 29 % pos., and 17 into the »inactive—healed cases of c. p.», with 12 % pos. agglutinations.

Among the 26 neg. cases within the group »severe—moderately severe cases» there are 2 which had typical c. p. in connection with gonorrheal infection, both cases showed neg. complement fixation reactions to gonococci, and the whole morbid picture for the rest tallies with a c. p. In addition to his c. p., one case had *hepatitis acuta*, which made its appearance after the specimen for agglutination had been taken. 3 cases had had their illness for less than 6 months, and one of these had also an AST value up to 880. There is nothing to add concerning the other 20 cases, except that 1 patient had had the illness for 17 years and 2 patients for 10 years.

Of the 53 cases within the group of »slight» cases of c. p., 10 had had their illnesses for

Table 2.

Diagnosis	Total no. of cases	No of pos. aggl.	% pos. aggl.	No. aggl. no. of cases	No. of agglutinations for the different serum dilution							
					1:20	1:40	1:80	1:160	1:320	1:640	1:1280	1:2560
Chronic polyarthritis. All cases. ....	224	130	58	28	17	22	27	76	36	13	4	1
Chronic polyarthritis. Moderately severe—severe cases .....	132	106	80	4	6	6	10	53	35	13	4	1
Chronic polyarthritis. Slight cases ...	75	22	29	17	9	12	15	21	1			
Chronic polyarthritis. Inactive—healed cases .....	17	2	12	7	2	4	2	2				
Spondylarthritis ankylopoetica .....	13	1	8	9	2	1			1			
Status post polyarthritidem acutam .	31	1	3	17	3	7	3			1		
The control group .....	102	2	2	71	19	9	1	2				

less than 6 months. 2 patients had also had *psoriasis*, and of these one had had his joint trouble for less than 6 months. In 1 case a typical c. p. had developed after a gonorrheal infection, and, as in the «severe» group, this case had a neg. complement fixation reaction to gonococci. In 1 case the c. p. had made its appearance after a trauma. There is nothing to add about the other 39 cases, apart from the fact that 1 patient had had his illness for 10 years, one for 14, and another for 20 years.

No definite difference emerged between the cases which had had an acute onset in comparison with those in which the first appearance was chronic, either in respect of the frequency of pos. agglutinations or of high titres.

In his investigations Kalbak (11, 24) found 79 %, Edström and Winblad (12) 76 % of pos. agglutinations, employing the same method, while, also with the same method and the same streptococci as the antigen, I found 58 %. On the other hand, if the group «severe—moderately severe» cases in my material is compared with those of the two earlier investigators, good agreement is met with.

Cecil and de Gara (9) also divided up their material of 268 cases into the groups «slight», «moderately severe» and «severe» cases, with 46.3, 68.8 and 65.8 % of pos. agglutinations respectively. Their division, however, is mainly based on the patients' capacity for work, and thus is not comparable with my division.

The *spondylarthritis ankylopoetica* group comprises 13 cases with 1 pos. agglutination, i. e. 8 %.

It should be noted that the pos. agglutination was met with in a patient who, in addition to his spondylarthritis, had a c. p. with unmistakable exacerbation in a number of joints. The agglutinations were carried out on 3 different occasions at intervals of 2 months and 1 month, and on every occasion gave a titre of 1:320. Among the neg. there was one further case with a morbid picture very like the abovementioned, but there the agglutination was neg. on 2 occasions.

Among 67 cases with spondylarthritis Dawson and co-workers (6) found 7.4 %, and among 16 cases Cecil and de Gara (9) found 6.2 % of pos. agglutinations. My results must be considered to tally well with these.

The group *status post polyarthritidem acutam* comprises 31 cases, with 1 pos. agglutination, i. e. 3 %.

The pos. agglutination was met with in a patient who had had repeated relapses of *rheumatic fever* and at the time of the examination was free of trouble and had a normal sedimentation rate and no objective joint changes.

Ragan and Tyson (10) give an account of a post-investigation of 142 cases with definite c. p. which had been treated with gold salts. In 17 cases the agglutination reaction had changed from pos. to neg.

Cecil and de Gara (9) describe 37 cases with c. p. which were examined before and after treatment with gold salts. 20 cases changed to neg. reactions. They found from the investigation that there is a connection between the duration of the illness, its degree of severity, the first improvement and change to a neg. reaction, so that slighter cases, shorter durations of the illness, and commencing improvements often exhibited changes to neg. reactions. On the whole they found the same conditions in 24 patients which had had other treatments, and arrived at the conclusion that gold salts treatment did not directly affect the formation of agglutinins against streptococci.

In this investigation the agglutinations were carried out in 40 cases of c. p. before and after treatment with gold salts. Of these 36 had pos. agglutinations before the beginning of the treatment, and 26 of them changed after the treatment to definitely neg. reactions. A reduction of the titre from 1 : 160 to 1 : 80 was not apprehended as a change to a neg. reaction. In one case the titre fell from 1 : 1280 to 1 : 320 and in another from 1 : 640 to 1 : 160. Eight cases exhibited unchanged titres, while in all the four cases which were neg. before the treatment began the titre increased, in one case from 0 to 1 : 160, and in three cases from 1 : 40 to 1 : 160. In one of the latter an unmistakeable disimprovement had also made its appearance. This case and the one in which the titre increased from 0 to 1 : 160 had received a total amount of gold which was considerably less than in the other cases.

In the majority of the cases in which the agglutination titre had definitely fallen or become neg., considerable improvements, both subjective and objective, had also made their appearance. The greatest reductions were exhibited by those who had had some complication or other during the gold salts treatment. Experience has also shown that, when such complications of c. p. make their appearance, a rapid improvement often sets in at the same time (21—23).

It should be mentioned that 2 cases, which developed exanthema and were improved but not entirely free of trouble after gold salts treatment, had agglutination titres of 1 : 320 and 1 : 160 respectively when discharged from hospital, and when they returned to the hospital after about 3 months, they were entirely free of trouble and had neg. agglutinations.

Agglutinations before and after physical treatment only were carried out in 8 cases, which all had pos. agglutinations before the treatment was begun. 5 of

them exhibited a change to neg. agglutinations after the treatment, 4 of them had also improved considerably. In one of the cases where the agglutination had not changed, an improvement had also set in.

It is impossible to draw any conclusions as to the relation between the agglutinations reaction and the treatment, as the results did not all point in the same direction, and the material is small.

In both this investigation and in earlier ones a definite connection could be proved between the streptococcus agglutination and c. p., especially in the cases of »severe—moderately severe» cases. Thus these patients would have had in their blood considerably increased quantities of antibodies, specific or unspecific, which led to pos. agglutinations with hemolytic streptococci.

### Summary.

1. The investigation comprised 224 cases of *chronic polyarthritis*, 13 cases of *spondylarthritis ankylopoetica*, 31 cases of *status post polyarthritidem acutam*, with 102 cases of non-rheumatic patients as control material. 58 % of the cases with definite c. p. exhibited pos. agglutinations with a  $\beta$ -streptococcus belonging to Group A, type 1, as the antigen, while in the control group only 2 % gave pos. agglutinations.

2. By dividing up the polyarthritis material into the groups »severe—moderately severe», »slight» and »inactive—healed» cases, the present author was able to show that within the »severe—moderately—severe» group 80 % showed pos. agglutinations, and that for this group there is a definite connection between the disease and the streptococcus agglutination, which tallies with earlier investigations.

3. The division into groups shows that, in slight cases of c. p. where there is a doubt as to the diagnosis when the reaction is neg., the reaction is of no help for the differential diagnosis, as this group only gave pos. agglutinations in 29 %.

4. Again, it appears that, in order to be able to make a comparison between different investigations, it is only necessary to take into consideration the definite diagnosis, but attention must also be paid to the degree of severity of the case, and to what stage the disease has advanced.

5. Further, it appears that sera from cases with *spondylarthritis ankylopoetica* only gave pos. agglutinations in 8 %, and finally.

6. That the group *status post polyarthritidem acutam* only gave pos. agglutinations in 3 %.

### References to the Literature.

1. Cecil, R. L., Nicholls, E. E. and Stainsby, W. I.: The American Journal of the Medical Sciences, 1931: 181: 12. — 2. Gray, J. W. and Gowen, C. H.: Ibid., 1931: 182: 682. — 3. Nicholls, E. E. and Stainsby, W. I.: Journal of Clinical Investigation, 1933: 12: 505. — 4. Dawson, M. H., Olmstead, M. and Boots, P. H.: Journal of Immunology, 1932: 23: 187. — 5. Dawson, M. H., Olmstead, M., Boots, P. H. and Jost, E. L.: Ibid., 1934: 27: 355. — 6. Dawson, M. H., Olmstead, M. Boots, P. H. and Jost, E. L.: Nordisk



Medicinsk Tidskrift, 1936: II: 1408. — 7. Mc Ewen, C., Chasis, H. and Alexander, R. C.: Society for Experimental Biology and Medicine, 1935: 33: 133. — 8. Keefer, C., Myers, W. and Oppel, Th.: Journal of Clinical Investigation, 1933: 12: 267. — 9. Cecil, R. L. and de Gara, P. F.: The American Journal of the Medical Sciences, 1946: 211: 472. — 10. Packalén, Th.: Nordisk Medicin, 1943: 17: 99. — 11. Kalbak, K.: Ibid., 1946: 31: 1937. — 12. Edström, G. and Winblad, S.: Ibid., 1947: 33: 506. — 13. Thulin, K. E.: Ibid., 1947: 33: 508. — 14. Olhagen, B.: Ibid., 1947: 33: 509. — 15. Hedlund, P.: Ibid., 1947: 33: 510. — 16. Winblad, S.: Om sjukdom och sjukvård: Studier tillägnade Malte Ljungdahl, 1947. (On disease and the care of the sick: Studies dedicated to Malte Ljungdahl.) — 17. Thulin, K. E. and Berglund, K.: Nordisk Medicin, 1947: 34: 889. — 18. Ragan, Ch. and Tyson, T. Ll.: The American Journal of Medicine 1946: 1: 252. — 19. Knutsson, F.: Acta Radiologica, 1943: 14: 121. — 20. Bohman, F.: Nordisk Medicin, 1944: 21: 287. — 21. Sundelin, F.: Die Goldbehandlung der chron. Arthritis, Lund 1941. — 22. Sundelin, F.: Nordisk Medicin, 1944: 21: 283. — 23. Sundelin, F.: Ibid., 1947: 37: 307. — 24. Kalbak, K.: Acta med. scand., 1948: 130: 358. — 25. Thulin, K. E.: Gradualavhandling, Lund 1948. (Doctor's Thesis.)

---

Aus der I. Med. Universitätsklinik, Budapest.  
(Direktor: Prof. Dr. Stefan Rusznyák.)

## $Tm_{NH_4}$ ; Beziehungen zwischen renalen Synthesen und anderen Tubularfunktionen.

Von

Dr. M. FÖLDI, Dr. ST. LAZAROVITS und Dr. G. SZABÓ.

(Bei der Redaktion am 6. August 1949 eingegangen.)

Seitdem Smith und seine Schule die Begriffe der maximalen in der Zeiteinheit resorbierten Zuckermenge ( $Tm_g$ ) und secernierten para-amino-Hippursäure ( $Tm_{pah}$ ) als Mass des resorbierenden und secernierenden Nierenparenchyms in die Nierenphysiologie einführte, befassten sich mehrere Arbeiten mit der Frage der *Kompetition*: d. h. mit den Beziehungen zwischen  $Tm_g$  und  $Tm_{pah}$  einerseits und *verschiedener* Resorptions- und Sekretionsmaxima andererseits. Wir wissen heute, dass sämtliche Stoffe, welche durch eine tubuläre Sekretion ausgeschieden werden, sich gegenseitig verdrängen (z. B.: PAH-Diodrast-Phenolrot-Penicillin). Es ist bekannt, dass es verschiedene resorbierte Stoffe gibt, welche die Resorption anderer Stoffe hemmen (z. B.: Glukose — andere Zucker; Vitamin C — Kochsalz, usw.). Und schliesslich besteht zwischen Glukose-Resorption und PAH-Sekretion eine gegenseitige Depression.

Ryberg (1) zeigte vor kurzem, dass während einer Azidose die  $NH_4$ -Synthese in der Niere sowie beim Menschen als beim Hunde einen maximalen Wert erreicht, der vom Grad und von der Dauer der Azidose unabhängig ist. Die *Ammoniak-Synthese*, die nach neuen Untersuchungen von Van Slyke (2) aus Glutaminsäure geschieht, ist *ausschliesslich eine Funktion der Niere*, und ist daher zur Untersuchung der Synthetisierungsarbeit der Tubuli — im Gegensatz zur Hippursäure-Synthese — sehr geeignet.

Wir konnten Ryberg's Ergebnisse bestätigen; die Ammoniakausscheidung erreicht während einer Azidose einen maximalen Grad. Wir empfehlen daher, dass die maximale  $NH_4$ -Ausscheidung —  $Tm_{NH_4}$  — als Mass des synthetisierenden Nierenparenchyms in die Nierenphysiologie eingeführt werden soll.

In dieser unserer Arbeit befassen wir uns

- 1) mit der Wirkung von Fermentgiften auf die  $\text{NH}_4$ -Synthese und
- 2) mit den Beziehungen:
  - a)  $\text{NH}_4$ -Synthese—Hippursäuresynthese,
  - b)  $\text{NH}_4$ -Synthese—PAH-Sekretion,
  - c)  $\text{NH}_4$ -Synthese—Glukoseresorption.

*Methodik:* Wir arbeiten am Menschen und am Hunde. Am Menschen verursachten wir eine Azidose mit ketogener Diät und  $\text{NH}_4$  Cl-Verabreichung, am Hunde mit HCl-Belastung. Den Grad der Azidose beurteilten wir mit Hilfe des Van Slyke-schen Verfahrens zur Bestimmung der Alkalireserve.  $\text{NH}_4$  im Urin wurde nach Van Slyke (2) bestimmt. Die endogene Kreatinin-Clearance diente als Mass der Glomerularfiltration.

## 1. Die Wirkung von Fermentgiften auf die $\text{NH}_3$ -Synthese.

a) *Versuche mit Phloridzin:* Wir arbeiteten mit einer 1 ‰-en wässrigen Phloridzin-Lösung, die wir intravenös verabreichten. 10—20 ccm einer solchen Lösung verursacht bereits beim Menschen eine beträchtliche Zuckerausscheidung — allerdings keine totale Hemmung der Zuckerresorption. Wir fanden, dass das Phloridzin in solchen Dosen keinerlei Wirkung auf die  $\text{NH}_4$ -Synthese ausübte. 5—10-fache Dosen setzten die Ammoniakausscheidung in *geringem* Masse herab (siehe Tabelle No. I). Der Umstand, dass relativ hohe Dosen zur geringen Depression der  $\text{NH}_4$ -Synthese erforderlich sind, zeigt, dass die Phloridzin-Wirkung im Falle der  $\text{NH}_4$ -Synthese eine unspezifische ist. Wir möchten darauf aufmerksam machen, dass das Phloridzin auch die para-amino-hippursäure-Sekretion vermindert (3); auch diese Wirkung wird als eine unspezifische aufgefasst.

b) *Versuche mit Chinin:* Wir injizierten Hunden 0.5 g Chininum bihydrochloricum intravenös und fanden, dass das Chinin, das, wie bekannt, viele Fermente hemmt, die Ammoniaksynthese stark *herabsetzt*: offenbar hemmt es auch die Glutaminase. (Siehe Tabelle No. II.)

## 2. Beziehungen zwischen $\text{NH}_4$ -Synthese und anderen Funktionen des Nierenepithels.

a) *Ammoniaksynthese—Hippursäuresynthese.* Injiziert man beim Menschen oder beim Hunde Natrium benzoicum, so steigt, wie bekannt, die Hippursäure-Ausscheidung im Harn. Hippursäure wird aus Benzoessäure und aus Glykokoll beim Menschen nicht nur in der Niere, sondern auch in der Leber synthetisiert, deshalb eignet sich die Prüfung der Hippursäure-Synthese als Nierenfunktionsprüfung nicht; man müsste dazu auch die Blutkonzentration der Hippursäure bestimmen. (Deshalb eben wählten wir als Mass des secernierenden Nierenparenchyms das Ammoniak, das ausschliesslich in der Niere synthetisiert wird.) — Unsere Erwartung war, dass zwischen den beiden renalen Synthesen eine Konkurrenz besteht, d. h.,

dass wir nach einer Injektion von Natrium benzoicum ein Sinken der Ammoniakausscheidung finden würden. Es zeigte sich aber, dass die Ammoniakausscheidung nach Injektion von 10 ccm 20 %-iger Na-benzoicumlösung nie sank — im Gegenteil, in der Mehrzahl der Fälle wurde sie eher *erhöht*. (Siehe Tabelle No. III.)

In Kontrollversuchen injizierten wir mit dem Na-Gehalt der verabreichten Na-benzoicum-Lösung äquivalente Mengen Na in Form einer 10 %-igen Kochsalzlösung um die Möglichkeit auszuschliessen, dass die Erhöhung der Ammoniaksynthese dem Na und nicht der Benzoesäure zuzuschreiben sei: die Kochsalzlösung hat die  $\text{NH}_4$ -Synthese nicht erhöht. (Siehe Tabelle No. IV.)

b) *Ammoniaksynthese und tubuläre (PAH) Sekretion*. Wir injizierten beim Menschen und beim Hunde grosse Mengen para-amino-Hippursäure intravenös (2–3 g). Wie Tab. No. V. zeigt, lässt die tubuläre Sekretionsarbeit die Ammoniaksynthese unbeeinflusst.

c) *Ammoniaksynthese und tubuläre (Dextrose) Sekretion*. Durch grosse Mengen einer intravenös injizierten hypertonen Dextrose-Lösung wird die  $\text{NH}_4$ -Synthese nicht herabgesetzt. (Siehe Tab. No. VI.)

Es sind weitere Untersuchungen im Gange, um hormonale Einflüsse auf die Ammoniaksynthese abzuklären.

### Summary.

$\text{Tm}_{\text{NH}_4}$  is recommended as a measure of the synthesizing tubular mass. — There is no competition between ammonia synthesis and other functions of the renal parenchyma: Hippuric acid synthesis, para-amino-hippuric acid secretion and glucose reabsorption. Hippuric acid synthesis seems rather to increase ammonia formation in the kidney; chinin and phloridzin depresses ammonia synthesis.

### References.

1. Ryberg: On the formation of Ammonia in the kidneys during acidosis. Acta Physiol. Scand. 15, 114 (1948). — 2. Peters and Van Slyke: Quantitative Clinical Chemistry. Baltimore 1946. — 3. Selhurst: Amer. J. Physiol. 182, 142 (1944).

Tabelle No. I.  
Einfluss von Phloridzin.

Fall No.	Periode	V	C <sub>K</sub>	NH <sub>4</sub> mg/min.	Res. alkali	Bemerkungen
396 48. XII. 13.	1	0.81	56	1.01	41.6	
	2	0.91	66	1.06		45 cm 1 ‰ phlorid. i.v.
1817 48. XII. 17.	1	7.1	108	1.06	46.4	
	2	7.5	94	1.05		40 cm 1 ‰ phlorid. i.v.
1870 49. I. 29.	1	3.0	80	0.940	38.5	
	2	3.9	80	0.740		
	3	11.3	88	0.745		200 ccm 1 ‰ phlor. i.v.
	4	16.0	90	0.670		
VIII/1866 49. I. 27.	1	5.9	36	0.446	36.8	
	2	6.0	34	0.560		
	3	6.8	35	0.440		30 cm 1 ‰ phlorid.
	4	6.0	32	0.450		
	5	6.0	32	0.450		
VIII/1869 49. I. 29.	1	4.8	35	0.448	37.0	
	2	4.3	29	0.402		
	3	4.75	27	0.376		60 cm 1 ‰ phlorid. i.v.
	4	5.2	23	0.331		
	5	4.85	21	0.324		
VII/1864 I. 26.	1	4.2	15	0.435	39.5	
	2	1.9	14	0.380		
	3	1.7	13	0.350		30 cm 1 ‰ phlorid. i.v.
	4	2.7	13	0.380		
	5	1.2	12	0.315		
VII/1866 I. 27.	1	5.1	14	0.390	40.0	
	2	4.4	12.4	0.330		30 cm 1 ‰ phlorid. i.v.
	3	3.2	12.5	0.280		
	4	1.6	11.0	0.235		
	5	2.3	10.0	0.214		

<sup>1</sup> V: Harnmenge pro Minute.

C<sub>K</sub>: Kreatinin-Clearance.

Protokollnummern mit römischen Zahlen bedeuten Versuche am Hunde.

— — — : trennt Perioden vor und nach der Injektion.

Tabelle No. II.  
Einfluss von Chinin.

Fall No.	Periode	V	CK	NH <sub>4</sub> mg/min.	Bemerkungen
VII/1890 II. 11.	1	4.13	9.5	0.380	1 ccm 25 % chinin i.v.
	2	2.34	13.7	0.500	
	3	0.22	8.3	0.167	
	4	0.10	8.3	0.166	
VII/1890 II. 12.	1	4.85	14	0.346	1 ccm 25 % chinin
	2	4.85	13.5	0.213	
	3	1.25	13	0.146	
	4	0.9	8.5	0.135	
VIII/1890 II. 12.	1	2.24	25	0.522	2 ccm 25 % chinin
	2	0.69	21	0.310	
	3	0.4	24	0.460	
VIII/1891 II. 12.	1	5.8	34	0.750	2 ccm 25 % chinin
	2	4.0	34	0.480	
	3	0.425	18.5	0.106	
	4	0.133	18.5	0.185	
VII/1906 II. 22.	1	2.07	11	0.390	Narconumal Nar- kose 0.5 ccm 25 % chinin
	2	0.12	10.7	0.060	
	3	0.08	9.8	0.104	
VIII/1906 II. 22.	1	3.5	22	0.510	Narconumal Nar- kose 0.91 ccm 25 % chinin
	2	2.8	20	0.440	
	3	0.36	21	0.284	
	4	0.28	21	0.278	

Tabelle No. III.  
Einfluss von Benzoesäure.

Fall No.	Periode	B	Ck	NH <sub>4</sub> mg/min.	Res. alkali	Bemerkungen
1820 48. XII. 27.	1	6.85	95.	0.90	48.5	20 ccm 20 % Na benz.
	2	3.7	97	1.14		
	3	1.97	82	1.00		
	4	2.7	82	1.08		
1821 48. XII. 28.	1	8.1	89	0.91	48	20 ccm 20 % Na benz.
	2	1.66	100	0.91		
	3	4.0	88	0.97		
1819 48. XII. 23.	1	1.9	92	1.30	40.4	20 ccm 10 % Na benz.
	2	7.2	92	1.39		
	3	14.0	115	1.90		
1823 XII. 30.	1	3.4	89	0.69	47.4	20 ccm 20 % Na benz.
	2	14.2	103	0.70		
	3	11.0	103	0.81		
1878 49. II. 3.	1	4.6	89	0.675	46.2	20 ccm 20 % Na benz.
	2	17.8	87	0.676		
	3	6.6	76	0.810		
1883 49. II. 7.	1	4.0	68	0.320		10 ccm 20 % Na benz.
	2	11.2	70	0.386		
	3	5.7	77	0.670		
VII. II. 12.	1	3.62	10.6	0.217	38.7	5 ccm Na benz.
	2	2.68	11.5	0.201		
	3	1.21	12	0.266		
VIII. II. 14.	4	0.75	11.3	0.340	40.6	10 ccm 20 % Na benz.
	1	3.65	24	0.365		
	2	3.0	22.5	0.300		
	3	3.35	21	0.520		
	4	3.2	26	0.665		

Tabelle No. IV.  
Einfluss von NaCl.

Fall No.	Periode	V	CK	NH <sub>4</sub> mg min.	Res. alk.	Bemerkungen
VII/1903 II. 17.	1	3.4	13.8	0.204		
	2	3.4	12.6	0.240		
	3	0.5	12.0	0.238		1.6 ccm 10 % Na Cl.
1820 XII. 27.	1	6.85	95	0.900		
	2	3.7	97	1.140		
	3	2.0	82	1.000		10 ccm 10 % Na Cl.
VIII/1903 II. 17.	1	4.0	27.7	0.514		
	2	3.7	26.6	0.506		
	3	3.1	25.6	0.375		3.2 ccm 10 % Na Cl.
	4	2.9	25.2	0.405		

Tabelle No. V.  
Einfluss von Para-amino-Hippursäure.

Fall No.	Periode	V	CK	NH <sub>4</sub> mg/min.	Res. alkali	Bemerkungen
399 XII. 14.	1	3.4	63	1.420	41.6	
	2	4.7	65	1.180		
	3	1.9	54	1.140		2 g PAH. i.v.
1819 XII. 23.	1	1.9	92	1.300	40.7	
	2	7.3	92	1.390		
	3	3.4	88	1.200		2 g PAH. i. v.
1874 II. 2.	1	3.66	83	0.585		
	2	13.7	93	0.548		
	3	10.5	86	0.608		3 g PAH. i.v.
1886 II. 8.	1	3.34	87	0.367	46.5	
	2	12.8	82	0.368		
	3	4.9	78	0.497		3 g PAH. i.v.
1892 II. 12.	1	8.5	98	0.408	46.4	
	2	9.7	84	0.446		
	3	4.8	82	0.525		3 g PAH. i.v.
	4	2.0	80	0.446		
VII. 1897 II. 15.	1	3.6	26	0.348	40.6	
	2	3.4	29	0.326		
	3	4.1	28	0.476		2 g PAH. i.v.
	4	3.4	31	0.442		
VIII. 1897 II. 15.	1	4.7	14	0.266	38.7	
	2	2.9	12	0.215		
	3	0.6	11	0.171		1 g PAH.
	4	1.0	13	0.180		



Tabelle No. VI.  
Einfluss von Glucose.

Fall No.	Periode	V	Ck	NH <sub>4</sub> mg/min.	Res. alkali	Bemerkungen
391 XII. 14.	1	1.62	57	1.200	41.5	400 ccm 20 % glucose
	2	0.61	46	0.980		
	3	3.4	63	1.420		
	4	4.7	65	1.180		
1819 XII. 22.	1	1.9	92	1.300	40.6	150 ccm 30 % glucose
	2	7.3	92	1.390		
	3	18.6	105	1.590		
1826 I. 4.	1	3.1	97	0.590	46.2	150 ccm 40 % glucose
	2	5.9	97	0.760		
	3	6.4	116	0.600		
1889 II. 11.	1	5.4	98	0.547	47.1	250 ccm 30 % glucose
	2	16.1	91	0.484		
	3	12.7	107	0.556		
	4	14.4	97	0.636		
1886 II. 8.	1	3.3	87	0.367	55.8	250 ccm 30 % glucose
	2	12.8	82	0.368		
	3	17.3	85	0.484		
1874 II. 2.	1	3.7	83	0.585	43.3	200 ccm 30 % glucose
	2	13.7	93	0.548		
	3	12.9	88	0.776		

From the First Medical Clinic, Sahlgrén's Hospital, Gothenburg, Sweden.  
(Head: Professor M. Odén, M. D.)

## Intermittent Claudication and Vascular Spasm.

### III. A New Theory to Explain some Phenomena in Intermittent Claudication often Interpreted as being Due to Vasospasm.

By

TORSTEN LINDQVIST, M. D.

(Submitted for publication November 15, 1949.)

---

#### Introduction.

Opinions are still far from unanimous regarding the question of whether vasospasm plays any part in producing the symptoms in intermittent claudication or not. In a previous publication (Lindqvist [1]), I have sketched the historical background of this problem. Lewis, Pickering and Rotschild (2), and quite recently, Ejrup (3), have published exhaustive papers on the whole question, and there is therefore no need for me to go into this aspect further here.

In my two previous publications on this question (Lindqvist [1, 4]), I came to the conclusion that, in some cases at least, the presence of vascular spasm must be assumed, but that the spasm cannot be the cause of the pain. The reason why I did not consider it advisable to refute the theory of vasospasm was that I could find no other explanation for the decrease in the oscillations in the leg after exercise that I had noted in some patients with intermittent claudication. Most puzzling of all were my observations in a patient (Lindqvist [4]) in whom there was marked reduction in the oscillations over the lower part of the thigh and over the calf after exercise but in whom no signs of structural disease of the arteries could be found either by arteriographic examination, oscillometric recordings, with the patient at rest, or by measurement of the skin temperature by adequate methods.

Continued observation of this patient has revealed, however, that it was a question of progressive obturation of the lower part of the aorta, this diagnosis being finally verified by aortography (Lindqvist [5]). This finding caused me to revise my attitude with regard to the possibility of vascular spasm in claudication. In the meantime I had also made other observations that suggested a new approach, and the results are discussed in the present paper.

My lines of approach in my new investigations were the following. André-Thomas (6, 7, 8), who seems to have been the first to record reduction of the oscillations in the leg in connection with exercise in patients with intermittent claudication, considered this reduction to be a regular occurrence. His material was small, however. Leary and Allen (9) noted a reduction in the oscillations in working limbs in some cases of claudication, but in most cases they found an increase. Ejrup (10, 11, 12) on the other hand, considers that a decrease in the size of the oscillations after exercise is a consistent finding in arterial occlusion due to structural disease. His statements are based on a very large series of cases, but, as may be seen, they are in opposition both to my earlier findings (Lindqvist [1, 4]) and to those of Leary and Allen, who believe that in some cases there occurs a decrease and in others an increase in the oscillations in the affected leg in intermittent claudication. As different investigators have come to different conclusions it thus seemed logical to suspect that some difference in experimental method might be the explanation of these discrepancies. André-Thomas, in his investigations, placed the cuff just above the malleoli. Ejrup chose the same position as his normal method, particularly in his earlier studies, while in special cases he placed the cuff in another position. Leary and Allen, on the other hand, applied the cuff around the upper part of the calf, as I also have done in most of my earlier investigations.

In order to ascertain whether the position of the cuff is in any way responsible for producing an increase or a decrease in the oscillometric tracings in connection with exertion I have carried out oscillometric examinations in a suitable series of intermittent claudication cases, on resting and working limbs, with the cuff placed on the uppermost part of the calf and also with the cuff directly above the malleoli. In all examinations I used a von Recklinghausen oscillometer with an alternating scale.

### Observations.

*Case 1. J. A. G. born 1887. A railway-station hand. Out-Patient Record No. 12893/44.*

In 1941, he was treated at the hospital for arteriosclerosis in the right leg associated with severe pain in the foot. He suffered from severe intermittent claudication in the left calf from the middle of 1944. When he was examined in November 1944 he could not walk more than 40—50 meters without experiencing severe pain. The pulse was not palpated anywhere in the left leg. When he was resting, an oscillometric examination, with the cuff applied around the upper part of the calf, yielded tracings only 1.2 scale units<sup>1</sup> in height, in other words, a pathologically low value. After he had walked 150 meters, suffering severe pain in the calf and foot, the tracings from the calf increased to twice the height of those obtained from the resting limb; the blood pressure was also higher. When he was resting, the oscillometric tracings from a point just above the malleoli on the left side were 0.3 high. After the above-mentioned exercise, no oscillations at all could be demonstrated with the cuff applied in this position.

The oscillations in the calf of the resting limb were so small that some structural obstruction was obviously present higher up. On exertion the oscillations in the calf increased but disappeared entirely just above the malleoli.

<sup>1</sup> Throughout the whole of this communication the figures describing the tracings refer to scale units of the von Recklinghausen apparatus.

*Case 2. E. L. born 1892. A municipal council worker. Out-Patient Record No. 206/45.*

In April 1944 he suddenly began to experience pains in his left calf and foot, after walks of about 5 minutes' duration. Measurements of the skin temperature in the toes with the body temperature raised, carried out at the beginning of May 1944, revealed that the vessels in the left leg were seriously occluded. Because of this, a lumbar sympathectomy with removal of the sympathetic chain and three ganglia on the left side was performed on June 12, 1944 (Dr. S. Lembke). After the operation he was improved, but not wholly relieved from the pain.

At an oscillometric examination on Jan. 8, 1945 fairly small tracings reaching no higher than 1.5 were obtained when the patient was at rest and the cuff was placed around the left calf; this was obviously a pathological state of affairs in view of the fact that the oscillations on the right side were 5—6 in height. After a walk, during which he experienced much pain in the calf and foot, the tracings from the left calf increased in height, the maximum height being 2.5. In addition, the blood pressure was much higher. The highest tracings were obtained at a pressure of 160, after exercise, and at a pressure of 130, before exercise. When the cuff was applied just above the malleoli the tracings reached a maximum height of 0.8 with the patient at rest. After exercise, a maximum tracing of 0.7 was obtained, but only when the pressure was much lower than it had been before. Before exercise, the best tracings were obtained at 100—110 mm Hg, and after exercise, at 60—80 mm Hg. Both the systolic and the diastolic pressures were lowered. After 5 minutes' rest the tracings had increased in size again, reaching a height greater than that observed before the exercise. The highest tracings reached a level of 1.2. After a fresh period of exercise the highest tracings were only 0.5 in height. Repeated examinations yielded, in the main, the same results.

Exposure of the artery high up in the thigh, for the purpose of an arteriographic examination, revealed that the vessel was narrowed to a marked degree. An attempt at arteriography was unsuccessful.

In this case, the oscillometric tracings from the left calf, with the patient at rest, were so small that an obstruction higher up seemed likely; this suspicion was confirmed when the artery was exposed. After exercise the oscillations in the calf increased and the blood pressure in the upper part of the calf rose. In the lower part of the calf, on the other hand, the size of the oscillations decreased and the blood pressure dropped with exercise.

*Case 3. I. J. A carpenter, aged 59. Out-Patient Record No. 205/45.*

He had been troubled for 5—6 years by typical intermittent claudication pains in both legs. Measurement of the skin temperature in the toes, with the body temperature raised, revealed that there was an obturating process in the vessels in the left leg. Arteriographic examination carried out at the beginning of 1944 proved that advanced arteriosclerosis was present, the contrast medium being completely blocked for a segment 6—7 cm in length in the left thigh and a fairly weak system of collateral vessels having developed. Lumbar sympathectomy on the left side was performed in April 1944 (Dr. E. Moberg). The operation brought no relief.

At oscillometric examinations made on repeated occasions during the autumn of 1944 and the spring of 1945, oscillations 2.2 high were obtained from the upper part of the calf when the patient was resting. After a walk, during which he experienced severe pain in the calf, the pulsations in this area increased to 3.0 in height and the blood pressure rose. When the cuff was applied at a point just above the malleoli the highest tracing reached 0.9 with the patient at rest. After exercise, the pulsations decreased noticeably, the maximum height of the tracings being 0.5, and both the systolic and the diastolic pressures dropped. After as short a rest as 4 minutes, however, the tracings were once again as high as before, and they continued to increase until, 12 minutes after the exercise, the highest

tracing had reached 1.9 (see fig. 1). At another examination, when more strenuous exercise had been taken, the tracings from the area above the malleoli dropped so low as to be hardly distinguishable.

In this case, there was thus an arteriographically demonstrable obstruction of the femoral artery with complete obturation of the artery. After exercise, the oscillations in the upper part of the calf increased and the blood pressure in this area rose. In the small of the leg, on the other hand, there was a decrease in the size of the oscillations and a drop in the blood pressure immediately after exercise, but after 4—5 minutes this decrease had already been replaced by an increase in the size of the oscillations.

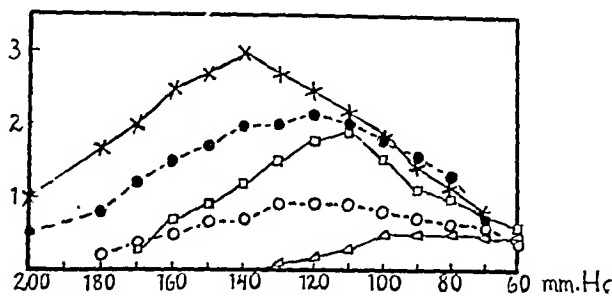


Fig. 1. Oscillometer readings in case 3.

- --- ● --- ● Oscillations in the upper part of the calf at rest.
- \* --- \* --- \* Oscillations in the upper part of the calf after work.
- --- ○ --- ○ Oscillations in the small of the leg at rest.
- ◁ --- ▷ --- ▷ " " " " " " after work.
- --- □ --- □ " " " " " " 12 minutes after work.

*Case 4. K. L., a warehouse assistant, aged 51. Out-Patient Record No. 12483/46.*

In the summer of 1945 he began to experience an aching pain in the lower part of his right leg after walking a few hundred meters. The pain disappeared as soon as he stopped walking. Examination at the beginning of September 1946 yielded oscillometric tracings of a maximum height of 6 from the upper part of the left calf when the patient was at rest, while the tracings from the right side, under the same circumstances, were only 1.5 high. After exercise, the tracings increased to 4 on the right side, and 15 minutes later they had reverted to their original value. When the cuff was placed above the malleoli on the right side the largest tracings were 1.2 at a pressure of 100—110, with the limb at rest. After a walk, the tracings showed a marked decrease. They were hardly distinguishable at a pressure of 70 mm Hg or more, and only at a pressure of 60 did they reach a height of 0.5. There was thus a striking decrease in both the systolic and the diastolic pressures. Within the course of 12 minutes the oscillometric values rose to the level observed before the exercise. (See fig. 2.) When the skin temperature in the toes was measured, with the body temperature raised, a fairly high degree of vascular occlusion was found in the right leg while the left leg was practically normal.

In this case, the presence of a structural obstruction in the vessels in the right leg, situated above the upper part of the calf, was definitely established. After exercise the oscillations showed a marked increase over the upper part of the calf but decreased in the region of the small of the leg.

*Case 5. A. B., a telegrapher, aged 35. Record No. 3203/47.*

In February 1947 he began to experience pains in the calves when he walked. After procuring foot-arch supports the pain disappeared from the right leg but became worse

in the left leg. In the autumn of 1947 his left foot began to feel numb in the region of the toes and it often became white and cold. At the end of November 1947 he developed severe pain in his left foot and was hospitalized on Dec. 3, 1947. He had also been troubled by several attacks of thrombophlebitis in the lower part of his left leg. On admission he had one fresh area of thrombophlebitis and another somewhat older one in his left foot. His pulse was not distinguishable in the dorsalis pedis artery or the posterior tibial artery on the left side. Measurement of the skin temperature in the toes, with the body temperature raised, as well as intravenous injection of tetraethylammonium bromide revealed the presence of a severe, obliterating vascular process in the left leg. The right leg was normal.

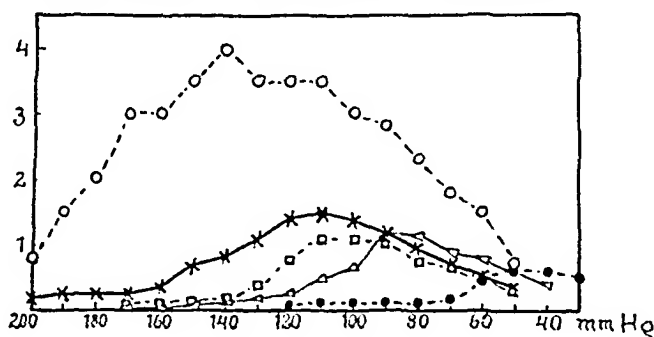


Fig. 2. Oscillometer readings in case 4.

\*—\*—\*—\* Oscillations in the upper part of the calf at rest.  
 ○—○—○—○ " " " " " " " " after work.  
 □—□—□—□ " " " small of the leg at rest.  
 ●—●—●—● " " " " " " " " after work.  
 ◁—◁—◁—◁ " " " " " " " " 12 minutes after work.

Arteriographic examination proved that the femoral and popliteal arteries and the anterior tibial artery were normal. Immediately below the origin of the latter artery the main trunk had become very thin and ended 3 cm below this point. Two large collaterals branched off at this spot, one running medially and one laterally. Neither the peroneal artery nor the posterior tibial artery were distinguishable. — Oscillometric examination with the cuff over the upper part of the calf yielded the maximum tracings, 5 scale units, when the patient was resting. After exercise, the blood pressure rose, and the maximum oscillations went as high as 6. Just above the malleoli the tracings went as high as 1.9 in the resting limb. After 10 minutes' rapid walking the tracings rose to 2.3, and the systolic blood pressure had increased while the diastolic pressure remained approximately the same as before.

Thus, we have here a case of Buerger's disease with organic obstruction of the vessels in the uppermost part of the left calf, confirmed by arteriography. When the cuff was placed on the uppermost part of the calf, for the oscillometric examination, the oscillations were larger after exercise than when the patient was at rest. The same conditions were found when the cuff was placed around the small of the leg.

*Case 6. J. S., a cook aged 54. Record No. 666/48.*

He had experienced pain in his left leg, on walking, for about two years. These symptoms had become accentuated during the past year. When in hospital in March 1948 he presented the following picture. When he was at rest the oscillations in the lower part of the left calf were decreased in size. The highest tracing was only 0.4. After a walk, during which he experienced much pain in the calf, the oscillations had decreased in size to such an extent that they were no longer recordable. For as long as 5 minutes after the exercise

no pulsations were distinguishable. After 9 minutes, small pulsations began to be noticeable, and after 15 minutes they had attained the same size as before the exercise. In the upper part of the left calf also, the oscillations were small, the largest reaching 0.8. After exercise, these oscillations increased, reaching a maximum of 1.3, and the blood pressure also rose. In the lower part of the thigh the tracings attained a maximum of 2.7 in the resting limb. Here also, there was an increase in the size of the oscillations and a rise in the blood pressure after exercise. Measurement of the skin temperature in the toes, with the body temperature raised, established the fact that there was moderate vascular occlusion on the left side, and a slightly lower degree of occlusion on the right side. Arteriographic examination after injection of contrast medium into the left femoral artery proved that the upper part of this artery was well filled with the contrast medium. About a palm's width proximal to the knee joint it was not visualized for a stretch of 2.5 cm. A large number of tortuous collaterals branched out from the area proximal to the point where the contrast substance ended, and through these collaterals the femoral artery distal to the obstruction was again being filled with contrast medium. Along the course of the femoral artery, both proximal and distal to the obstruction, there were numerous slack bulges extending from the wall into the lumen. The profunda branch of the femoral artery was normal. In the lower part of the leg, only two large arterial trunks instead of three were filled with contrast substance. The lumen of the peroneal artery was very narrow along a segment roughly 3.5 cm in length, and in this area a number of fine, tortuous collaterals were to be seen. Of the two arteries filled with contrast medium the medial one had somewhat irregular walls, especially in the proximal part of the lower leg. (See fig. 3.)

We thus have in this case complete obstruction, confirmed by arteriographic examination, within the lower part of the femoral artery, as well as a well-developed collateral system and arteriosclerotic changes in the arteries of the lower part of the leg. The oscillometric tracings obtained after exercise increased in size in the lower part of the thigh and the upper part of the calf while the oscillations disappeared completely in the lower part of the calf.

*Case 7. A. L., a postman, aged 29. Record No. 1038/48.*

Since the end of January 1948 he had experienced pain in his right calf after walking, especially up stairs. Examination at the hospital in April 1948 yielded the following information. The oscillations above the malleoli in the right leg, with the patient at rest, were only 1.7 high at the maximum as compared with 4.0 in the left. After exercise, during which the patient experienced the typical claudication pains, the oscillations in the right leg had become so small as to be no longer recordable. Five minutes after the termination of the exercise they had still not reached the level observed before the exercise; 12 minutes afterwards they were slightly larger than before the patient exerted himself, and as long as 20 minutes after the termination of the exercise the highest oscillations reached a level of 2.5 as compared with 1.8 before the exercise. In the upper part of the right calf the oscillations before exercise were roughly half the size of those in the left leg. After exercise these oscillations showed a slight increase, and the blood pressure rose. When the skin temperature in the toes was measured, with the body temperature raised, it was found that the blood flow to the toes of the right foot was inadequate. Arteriographic examination after injection of contrast medium into the right femoral artery revealed a local change in the wall of the popliteal artery extending for a distance of about 3 cm. The lumen in this part was narrowed into the form of a spindle, the artery being approximately 2 mm wide at the narrowest point. The vessel wall in this area was slightly irregular. No collaterals were distinguishable. The three large arteries in the leg, as well as the visible parts of the profunda branch of the femoral artery, were apparently normal. (See fig. 4.)

There was thus, in this patient, an arteriographically verified obstruction in the popliteal artery. The absence of collaterals gives rise to the impression that it might have been a question of spasm and not of structural change in the vessel wall, but the irregularities in the wall point strongly to an organic obstruction. Immediately below this obstacle the oscillations increased in size and the blood pressure rose after exercise, while in the lowermost part of the calf the oscillations disappeared when the patient exerted himself. When once the oscillations had begun to be recordable again they gradually increased in size and finally reached a level higher than before the muscular work.



Fig. 3. Arteriograms of the left leg in case 6.

Fig. 4. Arteriograms of the right leg in case 7.

*Case 8. A. A., a seaman, aged 26. Record No. 115/48.*

He had had syphilis in 1946. Since August 1947 he had had an aching pain in his left foot when he walked. He had a similar pain, though less severe, in his right foot.

While in hospital in January 1948 he presented the following picture. An oscillometric examination yielded no tracings from either side, when the cuff was applied above the malleoli. In the upper part of the left calf no tracings were obtained at a higher pressure than 110 mm Hg, and even at this pressure they were only just distinguishable. The highest tracings were obtained at a pressure of 70–80 mm Hg, being 0.4 at this pressure. After exercise, tracings were obtained even at 140 mm Hg. The largest oscillations were observed at 80–90 mm Hg, being 0.7 with this pressure. In the right calf, in which the oscillations before exercise were almost as small as on the left side, there was a much greater increase in the size of the oscillations following exercise. Arteriographic examination after injection of a contrast medium into the femoral artery revealed that this artery was about 4 mm wide and could be followed to a point roughly 18 cm proximal to the knee joint. From this point it continued in the form of two narrower vessels, the medial one of which was probably the *arteria genu suprema*. Further towards the distal aspect, around the knee joint, a weak system of collaterals was distinguishable, and in the lower part of the leg only one vessel between the tibia and fibula was filled down to the level of the syndesmosis. Aortographic examination yielded normal filling of the aorta and the upper part of the femoral arteries.



In this case, there was complete obstruction of the left femoral artery on a level with the point of origin of the arteria genu suprema. The oscillations in the upper part of the left calf increased noticeably after exercise. The conditions prevailing further towards the periphery could not be ascertained by oscillometry.

Other examples could be described. They are all characterized by the same features as those already reported. It appears that those mentioned provide sufficient material for discussion, and I have therefore refrained from quoting further cases.

Moreover, since I made my observations, Ejrup has published similar ones (3), of which I was unaware at the time I worked out my theory but which seem to furnish excellent evidence in support of it, although he himself interprets his findings in an entirely different fashion.

The fundamental points in my observations may be summarized in the following manner. *In cases of intermittent claudication in connection with structural arterial obstruction there occurs after exercise a marked fall in the blood pressure and a decrease in the size of the peripheral oscillations in the extremity. Proximally, though distal to the obstruction, there occurs a rise in the blood pressure and an increase in the size of the oscillations.*

### Discussion.

In all discussions on the occurrence of spasm in intermittent claudication a decision should be made with regard to the following questions.

#### 1. Where is the spasm situated?

Leriche (13) speaks of spasm in the collaterals. He has many followers in this respect. On what grounds, then, are the collaterals thought to be the site of the spasm? I have been unable to find any exhaustive discussion on this problem in the literature. Perhaps the advocates of this theory reason along the same lines as Ratschow (14, pp. 68—72), who believed that when arterial occlusion is present the symptoms are so severe that they can be explained in no other way than by assuming that the collaterals also become closed as the result of spasm. Certain arteriographic observations (see Ratschow l. c., also Sunder-Plassman, 15, pp. 76—77) would also seem to form a basis for this view. It would otherwise seem as though it were regarded as an axiom that the spasm must take place precisely in the collaterals. Many observers seem to follow the same line of reasoning as Ejrup (3, p. 240), when he declares that the idea of a »spasm distal to the stricture . . . would be unphysiologic». It would undeniably seem logical to imagine that a spasm, if it were present, would be located just in the collaterals.

The observations mentioned here prove very plainly that there is no spasm in the collaterals in connection with exercise. If a spasm were present there would be a decrease in the pulsations and a drop in the blood pressure over all the area distal to the obstruction. This is not the case. In case 5, I recorded the conditions prevailing exactly at the site of the collaterals. In this area also, the oscillations

were found to increase in size, and the blood pressure rose. Ejrup (3, pp. 240, 248) also found, both by direct palpation of collaterals and by tonoscillographic registration, an increase in the size of the pulsations in the collaterals.

My observations demonstrate that a drop in the blood pressure and a decrease in the size of the oscillations occurs first some distance below the obstruction, and that this distance is in some cases quite considerable. That an increase in the size of the oscillations and a rise in blood pressure may also occur below the obstruction is obvious from some of Ejrup's observations also (3, pp. 133, 157, 246). The significance of these cases seems to have escaped his attention, since in another connection he says that «in pathological cases no increase in pulsations takes place distal to the stricture» (l. c., p. 18), and this view plays an important part in his explanation of the cause of the decrease in the blood pressure level and in the size of the oscillations that occurs below the obstruction after exercise (*vide infra*).

*The theories based on the view that spasm in the collaterals is the cause of the symptoms in intermittent claudication must therefore be abandoned.* No theory can be acceptable that does not explain why blood pressure and pulsations increase strongly just below the obstructed area in connection with exercise but decrease further towards the periphery.

## 2. What is the mode of origin of the spasm?

Vasomotor reactions may be produced by direct local mechanical irritation, by nervous impulses, by physical changes (heat and cold), and by the action of chemical substances.

If there is a local lesion in the vessel wall, it is conceivable that this would directly provoke a reaction of spasm when extra stress is exerted on the vessel in connection with exercise, in the manner assumed by many investigators to occur in traumatic arterial spasm and the arterial spasm around an arterial embolus. (Cf. Allen, Barker and Hines [16].) All speculations of this kind are nullified by the fact that no spasm exists at the site of the obstruction.

Many authors, Leriche (13) and his school being perhaps the leaders in this respect, have emphasized the part played by the sympathetic nervous system in the occurrence of spasmodic constrictions of the blood vessels. With regard to the conditions prevailing in intermittent claudication I must repeat that in two of the cases described in this paper the decrease in the size of the oscillations and the drop in the blood pressure occurred peripherally in the extremities in connection with muscle work despite the fact that the examination was made on an extremity deprived of the sympathetic impulses from the central area by means of preganglionic sympathectomy. Ejrup (12, 3) also found that the results of oscillometric examinations on working limbs were not altered by sympathectomy. The sympathetic nervous system therefore cannot be held responsible for any significant degree of vasoconstriction observed in this disease. According to the experience of all investigators, the impulses transmitted to the vessels through the posterior roots are exclusively of a vasodilatory nature and are therefore out of the question as a

possible cause of vascular spasm. According to Fog's (17) opinion, it is necessary to assume that impulses are transmitted to the vessels in a muscle simultaneously with the motor irritation, in order to be able to explain the instantaneous changes in the blood flow, but here also it is a question of vasodilatory impulses (*vide infra*).

Cold can cause constriction of the fine arteries as well as a decrease in the oscillations in the legs (Silbert [18]), but lowering of the temperature of the extremity is, as we know, not such a consistent finding in exercise tests that it can be attributed any significance.

When discussing the effect of chemical substances we need to consider only the autogenous substances, since no foreign substances are used in the tests. The spasm is local, not general, and it is therefore necessary to deal only with the substances formed locally and having a local action. Comprehensive studies have been carried out on this problem, and they all show very much the same result. I refer here to the results of surveys by Kramer (19) and by Schenk (20). In muscular work, a vasodilatation immediately occurs. Fog (17) considers that this is due to nervous impulses, but another equally plausible explanation is in Kramer's opinion that it is produced chemically by acetylcholine which is liberated in connection with the irritation of the muscle, and which has a strong vasodilator action. Lactic acid and its phosphorylated combinations dilate the vessels. »Almost all substances taking part in work metabolism have a more or less pronounced vascular activity» (Kramer). It has never been found that a substance with a vasoconstrictor action has been formed in connection with muscular activity; all substances have, instead, a vasodilator effect. In claudication, there is, in all probability, an unsatisfactory flow of blood through the painful muscles, and it is therefore also necessary to have a clear conception of the formation of substances with vascular activity in tissues with poor circulation of the blood. It is evident from surveys by, among other authors, Rein (21) and Druckrey (22), that when the circulation is defective, substances with exclusively vasodilator properties are formed. Recent work by Folkow, Haeger and Kahlson (23) and by Folkow (24) make it probable that adenosinetriphosphate is the most potent of these substances.

Thus, as the substances formed in connection with muscular activity in muscles where the circulation is poor all dilate the vessels, there remains as the only explanation of the spasm the possibility that the vessels at the site of the stricture might react to the otherwise vasodilator substances by producing vasoconstriction. There would thus be an inverse reaction. This line of reasoning was originally suggested by Erb (25). Inverse reactions are not entirely unknown. In animal experiments, it has been demonstrated that the vessels react differently when the circulation is inadequate. Rein (21) summarizes his experiences as follows: »It is manifest that, in every area with a defective blood supply, whatever the cause may be, impulses from the central nervous system, reflex impulses and hormonal impulses are also without effect.» *Thus, the view that, in intermittent claudication, there is vasospasm provoked by locally formed substances is in direct opposition to the information hitherto acquired regarding the action of these substances.*

3. Is the »spasm» merely a consequence of altered hydrodynamic conditions?

A. Hustin's theory. The possibility that the alterations in the blood flow might be explained by the change in the hydrodynamic conditions, arising from the vascular obstruction, was first advanced by Hustin (26). He based his views on the results of certain model experiments. From these he found that if one has a relative obstruction in a vascular system through which a fluid is flowing, and if one dilates uniformly above and below the obstruction, the flow increases above and decreases below the obstacle. (For details, see the original article.) In this model experiment, however, a decrease in pressure occurs immediately below the obstruction. According to my observations, which I have described in this paper, there is, in claudication, an increase in the blood pressure and in the size of the pulsations immediately below the obstruction. Hustin's model thus does not have its counterpart in reality, and his deductions therefore cannot be transferred to conditions in life. His suggestion, however, opens up fresh lines of thought.

B. Ejrup's theory. Ejrup (3), who also raises objections against Hustin's view, puts forward a new theory, which he calls »the mechanical theory», in his latest publication. This came before my attention only after my paper was nearly finished, and it has had little influence on my viewpoints. His work is based on a large and very thoroughly analysed series of patients, and by and large there are no comments I feel disposed to make concerning his findings, but with regard to the interpretations he has put on some of his results I am not in agreement with him in certain important respects.

His theory may be stated briefly in the following paragraph.

The muscular work of an extremity presses the blood from capillaries and veins in a proximal direction. As a consequence of this, blood will be sucked to the muscle, which results, under normal conditions, in an increase in the blood flow. When the arteries are obstructed conditions are different. »An evacuation of the blood is assumed to take place distally to the stricture. — The stricture allows the passage of a certain amount of blood, but this cannot exceed a certain limit. It follows that when the muscle pumps blood from the capillaries to the veins and further proximally, a 'vacuum' develops which gives rise to a fall in pressure below the stricture. — The author looks upon these strictures as purely mechanical factors. — The so-called arterial spasm is invariably a consequence of the evacuation of blood peripherally to the stricture. — An active arterial spasm is highly improbable. — The vasoconstriction that occurs is interpreted by the author as passive vasoconstriction brought about by the evacuation of blood» (pp. 227—29). »A complete emptying occurs of all blood from the muscle and from the vascular bed distally to the stricture. This is manifested on the oscillogram by a fall both in the systolic and diastolic blood pressures. When the exercise ceases, the blood flows slowly through the narrow, pathologically changed vessels and collaterals. It takes some time to complete this process» (p. 18).

Against this theory I would raise the following objections.

If we count on 100 mm Hg as being the normal mean pressure in the aorta we get the following distribution for the blood pressure drop in different blood vessel areas (*c. g.* see Best and Taylor [27, p. 191]). From the aorta to the small arteries the pressure falls 20 mm Hg. In the arterioles the pressure drop is 50—60 mm Hg,

in the capillaries 15—20 mm Hg, and in the veins 10—15 mm Hg. When there is a relative obstruction — in the adductor canal, for instance — the following conditions may be expected to occur when the patient is at rest and the streaming of the blood is not decreased. At the obstruction a decrease in pressure reflects the increased resistance at this point. The arterioles dilate slightly in order that the blood flow, despite the smaller absolute pressure drop between the arteries and the veins, will be the same as if the obstruction had not existed. The resistance in the arterioles is thus lowered slightly.

(See the broken line in fig. 5.) Both Ejrup and I have made the following observations in working limbs. The pressure proximal to the obstruction is raised. Directly distal to the obstruction also, the pressure is higher than in the resting limb. The pressure is very low, distally, in the arteries in the lower leg. In the capillaries and veins the pressure is zero. In the arterioles, therefore, there is only a slight decrease in pressure. (See the dotted line in fig. 5.) This change in the relative pressure drop between arteries and arterioles may conceivably be explained in several ways, from the hydrodynamic standpoint. One

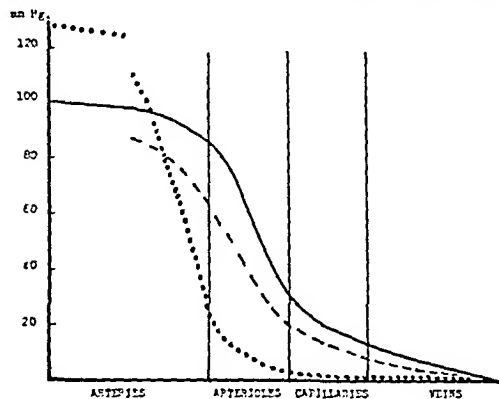


Fig. 5. Mean blood pressure in different parts of the vascular system.

— Normal subjects.

---- A case with arterial obstruction when at rest.

.... The same case after exercise.

explanation is that it may be due to a marked increase in the resistance in the arteries. This change in the resistance can only be ascribed to a decrease in the diameter of the arteries. Another possibility is that there may be a considerable decrease in the resistance of the arterioles. In that case, the arterioles must be markedly distended. A combination of these two possibilities is also conceivable. According to Ejrup's theory the vasoconstriction in the large arteries is purely passive, owing to the fact that the blood flows away to the arterioles and then on to the capillaries and veins more rapidly than it flows past the obstruction. But according to the relative pressure conditions that actually exist, the blood must flow rapidly in the large arteries, and slowly through the arterioles, if the latter are not dilated, which, according to the theory, they are not. This slow passage through the arterioles cannot, then, be used as an explanation of the rapid flow in the large arteries, as Ejrup does in his theory. Thus, the facts do not tally with this theory. — One may also express the matter in another way, by saying that the inconsiderable pressure drop in the peripheral end of the arterioles resulting from the evacuation of blood from capillaries and veins can hardly give rise in a wholly passive manner to the marked pressure drop in the proximal end of the arterioles that actually takes place.

Other objections may also be made. Emptying of the blood away from veins and capillaries when at the same time the inflow is obstructed causes the pressure to drop in the part of the arterial system situated nearest the periphery; *i. e.* the arterioles. The pressure difference between the arteries at the site of the obstruction



From the evidence obtained from the cases described in this paper, it is obvious that the drop in the pressure and the reduction of the pulsations after exercise in patients with claudication does not take place immediately below the obstruction but only at a considerable distance below it. Ejrup also observed an increase in the pressure and the pulsations below the stricture in a considerable number of cases, and I have not been able to find among his series of cases a single patient in whom the decrease in the blood pressure and the oscillations manifested itself immediately below the obstruction. This fact is entirely ignored in his comments on the pathogenesis, which seems instead to be founded on his view that «in pathological cases no increase in pulsations takes place distal to the stricture» (3, p. 18). It is, to me, incomprehensible how this fact could be brought into agreement with the evacuation theory. Admittedly, Ejrup has considered the possibility that this increase could be attributed to the increased flow of blood through the collaterals, but it is still not clear why the peripheral effect could not make itself felt also from that part of the collateral circulation which lies below the obstruction. The collaterals do not, in principle, occupy a unique position in any way.

The evacuation of blood must be greatest during the first muscle contractions, when there is much blood to express, and then become gradually less as the muscular activity proceeds. It is therefore to be expected, according to the evacuation theory, that the characteristic changes, a decrease in blood pressure and pulsations, would appear very shortly after the start of the muscle movements. In fact, the opposite is found, according to both Ejrup's and my own experience. This, in my opinion, does not fit in with the assumption that the evacuation of blood is the essential factor in the occurrence of this picture.

I would not deny that Ejrup, in his theory, has brought forward a factor that is of significance in explaining the changes in claudication, but his theory does not adequately explain the facts which he himself has demonstrated and which I also have been able to establish and verify; in many respects it is at variance with the facts.

C. My own theory. We must, therefore, endeavour to find a satisfactory explanation of these phenomena along other lines.

We find ourselves in something of a dilemma, since all previous experience points to the fact that in an extremity in which the circulation is poor there is a marked production of vasodilators in muscular activity. None the less, it is possible, in nearly every instance, to prove that there is a decrease in the blood pressure and pulsations in the peripheral part of the extremity. Under these circumstances we cannot just ignore both Ejrup's results and my own findings, which were based on a smaller series of cases, and explain all these cases as exceptions. (Cf. Leary and Allen [9].)

As I have pointed out further back, it cannot be denied that strong vasodilator forces arise in connection with muscular activity. We are therefore compelled to accept this fact and endeavour to ascertain how these forces affect the circulation.

Our task will be simplified if we postulate that the forces tending to cause vasodilatation during muscle work do not affect all parts of the arterial tree to

the same degree. The vasodilator substances are formed in the muscle during muscular exercise. It is therefore to be expected that they will act most powerfully on the small arteries and arterioles in the muscle. In the foot, there are very few muscles. The blood vessels running to this area chiefly supply the skin, which is more highly vascularized in the foot than in other parts of the leg. We may therefore assume that the arteries supplying the foot are exposed to vasodilator influences to a lesser extent than the muscular arteries. Even though there is a tendency to vasodilatation in the vessels of the foot, the circulation of the blood through this area can diminish when the marked dilatation of the muscle vessels in the calf appropriates such a large proportion of the increased circulation (increased to a certain extent but not in the same degree as in a normal subject) that nothing remains for perfusion of the foot. In this way, it would be possible to explain the conditions in the cases I have quoted where there was an obstruction in the popliteal artery or in the lower part of the thigh, and where the oscillations and blood pressure increased in the upper part of the calf but decreased or disappeared in the small of the leg. Corresponding observations mentioned by Ejrup could be explained in a similar fashion.

This explanation cannot, however, apply in general. Cases are also encountered in which the oscillations are found to be decreased and the blood pressure lowered even when the recordings are taken on the upper part of the calf or the lower part of the thigh. (See Lindqvist [1, 4], Ejrup [3].) The foot's share of the total blood flow past the obstruction is, in these cases, so small that it can be attributed little significance. Those areas that are situated just below the obstruction and that receive an added supply of blood, as well as those that lie further down and that become inadequately supplied, must be regarded as being subjected to vasodilator influences to an approximately equal extent.

It is dangerously easy to take it for granted that if the vasodilator forces are equally powerful in the whole of the vascular system peripheral to the obstruction the increased blood flow caused by exertion will distribute itself throughout this area in the same proportions as the blood that perfuses the limb when at rest. I was myself for a long time guilty of this false conclusion, which prevented me from making any further advance in my studies. A closer analysis will show that this premise is not correct.

Let us assume that we have two muscles of equal size that are supplied with blood through two arteries, one to each muscle, having the same calibre and originating from the same point. One of these arterial branches, however, is five times as long as the other. (See fig. 6.) Both muscles need the same circulation when at rest. The rate of flow in both arteries therefore needs to be the same. According to the law of Poiseuille, which applies to the flow in large but not in small vessels (Fåhræus and Lindqvist [32]), the velocity of flow depends on the pressure drop per length unit if the diameter is the same. In order to produce the same velocity of flow in both vessels, the pressure drop in the longer artery therefore needs to be five times as great as the drop in the shorter artery. This can be regulated by alterations in the pressure in the arterioles, whose combined pressure drop is much greater in relation to that in the afferent arteries. In order that these conditions may be fulfilled we may imagine a value of 100 for the average pressure at the common point of origin of the two arteries, of 98 at the point of entry of the shorter artery into the



muscle, and of 90 at the peripheral end of the longer artery. When in activity, the muscles need more blood. Let us assume that both muscles are doing an equal amount of work, and that the same increase in the supply of blood is needed in both cases. This may take place through an increase in the pressure at the dividing point, through a dilatation of the arterioles and reduction of the pressure in the peripheral end of the larger arteries, and, finally, through an increase in the diameter of the respective arteries. Dilatation of the arterioles takes place, in all probability, as the result of the action of vasodilator substances formed during the muscle work (*vide supra*). In normal cases, these factors can be balanced, so that the muscle will receive a sufficient flow of blood to wash away the vasodilator

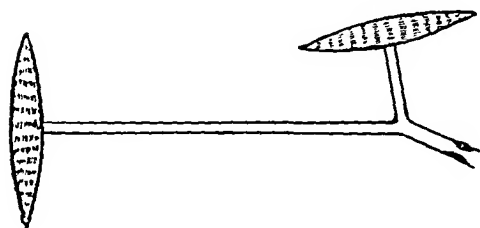


Fig. 6. For explanation see text.

substances formed during activity. But if the blood flow is hindered by the presence of an obstruction in the common afferent artery, the circulation of blood through the muscle will not be sufficient to remove the vasodilator substances rapidly enough, and they will therefore accumulate in the muscle in ever-increasing amounts. The arterioles (and perhaps the smaller arteries also) in the muscles will be affected and become still more distended. This leads to a drop in the pressure at the site of entry of the

main artery into the muscle. Let us assume that the situation has arisen that the mean pressure in the common artery has risen to 120 and that at the peripheral end of each artery it has dropped to 70 mm Hg. We thus have a pressure drop of 50 mm Hg in each artery. In the shorter artery this pressure drop applies to one length unit, in the longer artery to five length units. Thus, according to the law of Poiseuille, if we presume that the diameter of the arteries is unchanged, the velocity of flow in the shorter artery will be five times as great as in the longer one. Even if the total amount of blood were to increase to twice the original amount, we would have a decrease in the amount of blood supplied to the muscle that has the longer afferent artery. If the ratio between the two amounts of blood was 1 : 1 before exercise it would be 0.7 : 3.3 in the example selected here.

The better flow of blood in the muscle with the shorter artery must, however, to a certain extent flush away the dilating substances, so that the pressure drop in that muscle will not be as great as in the other one. There may even, perhaps, be no pressure drop at all, but instead a certain rise because of the increase above the obstruction, while the circulation will nevertheless be increased as the pressure rise in the central end of the shorter artery is greater than in the distal end.

In principle, we must admit that *if different parts of the vascular tree below the obstruction are subjected to the same vasodilator influences the circulation will be best in the areas having the shortest afferent vessels.* Despite the fact that the absolute pressure drop is greatest in the longer arteries the relative pressure drop is greatest in the short arteries. The latter thus receive a larger share of the total amount of blood, while the flow of blood through areas supplied by long arteries will deteriorate.

The conditions occurring in claudication in connection with muscular exercise could be satisfactorily explained in this way. According to both Ejrup's and my records, there is an increase in the pressure and pulsations after exercise immediately below the obstruction. This is in agreement with my theory, according to which there ought to be improved circulation in this area. Further towards the periphery the blood pressure and pulsations decrease. This also tallies with my theory.

Some objections that might be raised against this argumentation may be discussed here.

How can the following fact be explained? According to my reasoning, given in a preceding paragraph, a certain increase in pressure would occur in the proximal end of the longer of the two arteries, and a decrease in pressure in the distal end. This must give rise to an increase in the blood flow, according to Poiseuille's law, and not to a deterioration in circulation unless the lumen of the artery altered. A decrease in the lumen is thought by Ejrup to take place owing to the fact that the decreased pressure from within does not stretch the artery to such an extent, but if so, this is secondary to the pressure drop and therefore cannot be considered as a cause of the decreased blood flow. Direct observations by Fog (28, 29, 30) and by Folkow (31) in animal experiments show, however, that there is a dilatation of the arteries peripheral to an arterial occlusion, probably due to the fact that the decrease in impulses from the blood pressure causes a relaxation of the muscles of the vascular wall. This widening of the lumen should increase the blood flow still more. This objection would be correct, if the model sketched in figure 6 corresponded to reality in every respect. I have purposely simplified it, however, in order to be able to illustrate the fundamental principle as clearly as possible. In reality, arterial divisions branch off to muscles along the whole course of the long artery. The pressure drops gradually because of the outflow of blood, through these branches, into the dilated arterioles in the muscles situated most proximally, not because of the flow of blood to the muscle situated most peripherally, and it is therefore not necessary to suppose that there is any decrease in the lumen of its afferent artery.

I have demonstrated that some of Ejrup's observations cannot be made to fit in with his theory. It should be interesting to study how his findings can be applied under my theory.

He has found that immediately after exercise, some normal persons, especially those who are untrained, display inverted work oscillograms from the small of the leg but never from the upper part of the calf. This can be explained satisfactorily in two ways by my theory. Either by assuming that the vasodilator factors are less effective in the skin in the region of the foot than in the muscles, or by assuming that the dilatation of the arterioles in the muscles accommodates so much blood at this site that not even the increased total flow to the extremity suffices, and consequently muscles of the peripheral part also receive too little blood. (Cf. the statement made by Kramer [19], that the muscle always works with an inadequate circulation when performing strenuous exercise.)

In patients with claudication also, there is a rise in the blood pressure and pulsations both proximally and distally in the extremity when muscular activity begins. This fact, which, as we have seen, was difficult to explain on the basis of Ejrup's theory, agrees well with my view.

When the exercise ceases the production of vasodilator substances largely ceases. The increased flow of blood in the proximally situated muscles washes away the vasodilator substances and the circulation in these areas then decreases. It is only when this has taken place that the circulation improves in areas situated

further towards the periphery and the vasodilator substances are consequently washed away. The further towards the periphery an area is situated the longer will be the time elapsing before it regains its normal circulation. This is also in accordance with Ejrup's findings, «the more distal the area examined the longer the recovery phase» (3, p. 154). In some of the cases described in this paper (cases 2, 3, 7) we have seen that there was an increase in the blood pressure and pulsations in the small of the leg following the period of depleted circulation. This is quite comprehensible, by my theory. According to Ejrup's theory, this late peripheral vasodilatation is inexplicable, but it was recorded in some of his own observations.

This theory of mine helps to overcome the difficulties that have arisen in the discussion regarding the pathogenesis in intermittent claudication. Those investigators who hold that vasodilatation after muscular activity occurs in claudication also, have had to disregard the findings that undoubtedly point to decreased blood pressure and reduced pulsations in the peripheral parts of the affected limb. Those who have interpreted the decrease in blood pressure and pulsations as a sign of vascular spasm have not been able to explain how such a spasm could arise, seeing that all possible factors tend to produce a vasodilatation. According to Ejrup's theory, the arterioles have a «passive vasoconstriction», in spite of the strong vasodilator forces whose existence he himself mentions.

The solution of the problem that I have suggested demonstrates that it is precisely the dilatation of the arterioles that causes a reduction in the circulation in the peripheral areas of the affected leg, since the areas situated immediately distal to the obstruction appropriate such a large amount of blood, owing to their vasodilatation, that the periphery receives less. This deterioration in the circulation at the periphery is thus brought about as the result of, and not in spite of, the vasodilatation.

The dilatation of the arterioles, that I have advanced as being the cause of the circulatory disturbances, has this effect because of the fact that it calls for a considerable increase in the total flow of blood to the extremities. The evacuation of blood from the affected extremity, mentioned by Ejrup, is a factor pointing in the same direction. It may therefore be regarded as a contributory cause of the phenomena in question. But as I have shown, it cannot be taken as the sole explanation, and it is probably of secondary importance.

### Summary.

The paper discusses the question of whether vascular spasm is present in intermittent claudication or not. Oscillometric examinations prove that, in connection with muscular activity, there is a rise in the blood pressure and in the size of the pulsations immediately below the obstruction, but that practically without exception there is a considerable drop in the blood pressure and a decrease in the size of the pulsations in the peripheral areas of the extremity. The question of vascular spasm is discussed in the light of this observation. If such a spasm exists

it cannot be situated at the site of the obstruction or in the collaterals but must instead be located much further towards the periphery. All investigations point clearly to the fact that vasodilator substances only, not vasoconstrictor ones, are formed during muscular activity, especially in tissues where the circulation is poor. This fact is such strong evidence against the possibility of vascular spasm that one is compelled to wonder whether purely hydrodynamic factors might not cause an alteration in the distribution of blood in the extremities during exercise. Earlier theories advanced by Hustin and Ejrup are discussed and refuted. In the opinion of the author, the mechanism is, that the large accumulation of vasodilator substances arising in connection with muscular activity causes considerable dilatation of the arterioles. As the blood flow is lessened because of the organic obstruction, this dilatation causes a change in the distribution of the blood in accordance with hydrodynamic laws, with the result that the circulation becomes increased in the areas immediately below the obstruction, where the afferent arteries are short, and is depleted in those situated further towards the periphery. The two theories that up to the present have been at variance with one another, viz. the spasm theory and the vasodilatation theory, will thus be reconciled. The facts that have been advanced to prove the existence of vasospasm need not be branded as incorrect observations or as exceptions, but are fully explained by the assumption of a dilatation of the arterioles and the consequent alteration in the distribution of the blood in the extremities peripheral to the obstruction in connection with muscle work.

#### References.

1. Lindqvist, T.: *Acta med. Scandinav.* 121, 32, 1945. — 2. Lewis, T., Pickering, G. W. and Rotschild, P.: *Heart* 15, 359, 1931. — 3. Ejrup, B.: *Acta med. Scandinav. Suppl.* 211, 1948. — 4. Lindqvist, T.: *Acta med. Scandinav.* 121, 429, 1945. — 5. Lindqvist, T.: *Nord. Med.* 37, 321, 1948. — 6. André-Thomas et Levy-Valensi: *Paris Médical* 27, 58, 1918. — 7. André-Thomas: *Presse Méd.* 2, 1049, 1922. — 8. André-Thomas: *Les Phénomènes de Répercussivité*. Paris 1929. — 9. Leary, W. V. and Allen, E. V.: *Am. Heart J.* 22, 719, 1941. — 10. Ejrup, B.: *Nord. Med.* 27, 1498, 1945. — 11. Ejrup, B.: *Acta med. Scandinav. Suppl.* 206, 168, 1948. — 12. Ejrup, B.: *Svenska Läkartidningen* 45, 1, 1948. — 13. Leriche, R.: *The Surgery of Pain*. London 1939. — 14. Ratschow, M.: *Die peripheren Durchblutungsstörungen*. Dresden und Leipzig 1943. — 15. Sunder-Plassman, P.: *Durchblutungsschäden und ihre Behandlung*. Stuttgart 1943. — 16. Allen, E. V., Barker, N. W. and Hines, E. A.: *Peripheral Vascular Diseases*. Philadelphia and London 1946. — 17. Fog, M.: *Acta Psychiat. et Neurol.* 14, 11, 1939. — 18. Silbert, S.: *Am. Heart J.* 15, 265, 1938. — 19. Kramer, K.: *Verhandl. d. deutsch. Gesellsch. f. Kreislaufforsch.* 14, 66, 1941. — 20. Schenk, P.: *Ibidem* 14, 193, 1941. — 21. Rein, H.: *Ibidem* 14, 9, 1941. — 22. Druckrey, H.: *Ibidem* 14, 177, 1941. — 23. Folkow, B., Haeger, K. and Kahlson, G.: *Acta physiol. Scandinav.* 15, 264, 1948. — 24. Folkow, B.: *Ibidem* 17, 311, 1949. — 25. Erb, W.: *Deutsche Ztschr. f. Nerven.* 13, 1, 1898. — 26. Hustin, M. A.: *Mém. Acad. de chir.* 62, 828, 1936. — 27. Best, C. H. and Taylor, N. B.: *The Physiological Basis of Medical Practice*. 2nd Ed. Baltimore 1939. — 28. Fog, M.: *Arch. Neurol. & Psychiat.* 37, 351, 1937. — 29. Fog, M.: *J. Neurol. & Psychiat. N. S.* 1, 187, 1938. — 30. Fog, M.: *Arch. Neurol. & Psychiat.* 41, 260, 1939. — 31. Folkow, B.: *Acta physiol. Scandinav.* 17, 289, 1949. — 32. Fähræus, R. and Lindqvist, T.: *Am. J. Physiol.* 96, 562, 1931.

From the Finsen Laboratory, Copenhagen.

## Investigations upon the Mechanism of Indirect Warming.

By

ANTON FLØYSTRUP and ARNE P. SKOUBY.<sup>1</sup>

(Submitted for publication November 23, 1949.)

It has been previously demonstrated that the application of warmth to one part of the body may produce vaso-dilatation and a rise in temperature of the peripheral parts of the unheated limb (Sewall and Sandford 1890, Stewart 1911, Lewis and Pickering 1931, Gibbon and Landis 1932). Extirpation of the sympathetic innervation of a limb abolishes this indirect heating effect (Lewis and Pickering 1931, Vanggaard 1941). The response to the direct heating of one segment must therefore be produced either by an inhibition of vaso-constrictor or by a stimulation of vaso-dilator impulses to the vessels in the areas indirectly heated. The manner in which this action takes place has been investigated by several methods with divergent results.

By means of a water calorimeter Pickering (1932) demonstrated that the heat-loss from one hand is not increased, when the other hand is warmed at the same time as its circulation is occluded. Gibbon and Landis (1932) and Upprus, Gaylor and Carmichael (1936) found that occlusion of the circulation from a directly heated upper limb prevented the occurrence of a rise in temperature in the toes, and that a total paralysis of the lower limbs from transection of the spinal cord did not prevent a rise in temperature of the fingers, when the feet were warmed in a water-bath at 43—45°C. In contrast to these results, which seem to indicate a humoral transmission from the area of direct warming to the nerves supplying the vessels in the indirectly heated areas, Duthie and Mackay (1940) found that even when the circulation from the directly heated areas is blocked, an indirect heating can be produced. In experiments where this was not the case a rise in the temperature of the unheated limbs occurred 2—4 minutes after the blockade was abolished. From this it appears as though the reaction may be of neurogenic origin in all its phases.

The present paper seeks to elucidate which factors acting through sympathetic nerve cells produce a rise in temperature of the toes of limbs cooled by the method of Christiansen et al. (1939) when parts of the upper limbs are heated by the meth-

<sup>1</sup> Københavns Amts Sygehus, Hellerup (Denmark).

od of Gibbon and Landis. The purpose of the investigation is to create the necessary basis for understanding the reactions which occur, when this particular technique is employed as a test of function in the study of peripheral vascular disorders of unknown pathogenesis.

### Technique.

The experiments are carried out on normal subjects and include heating of parts of the upper limbs of varying extent in a water-bath at 43° C., heating of the hands during simultaneous cooling of the forearm or neck with ice-bags and occlusion of the circulation from the heated limb by means of an Esmarch's bandage.

The experiments are performed at a room-temperature of 18—20° C. The subject under investigation is seated with one leg enclosed, without touching the walls, in a copper box with a wall-temperature of 1° C. The space between the leg and the upper edge of the box is closed by means of a pillow. The temperature of the pulp of the great toe is measured by means of a thermo-couple and galvanometer as previously described (Skouby 1949).

### Results.

To discover whether with this technique a rise in the temperature of the toes can be produced by warming the hands, when the circulation from the upper limbs is blocked, the latent period is measured in ten normal subjects first without blocking and then with simultaneous occlusion of the circulation from the upper limbs for 10—15 minutes. The heating is continued after the end of the blockade either for a period corresponding to the observed latent period with intact circulation or until the onset of a rise in toe pulp temperature. The results are given in table 1, which shows that in none of the experiments did a rise in the temperature of the toe pulp occur during the blockade. In seven experiments the temperature rose after the blockade was lifted after an interval almost corresponding to the latent period observed under normal conditions. In 2 experiments the heating was abandoned when the normal latent period was exceeded but before the temperature had risen, and in one experiment the temperature rose more quickly (three minutes), in comparison with the latent period under normal conditions (ten minutes). Since all sensation of pain in the occluded limb disappears as soon as the circulation is restored, and yet in nine out of ten experiments the pulp temperature did not rise within a short time after the release of the circulation from the warmed tissues, the rise in temperature can hardly be ascribed to a neurogenic mechanism, suppressed during the blockade by a vaso-constriction set up by the pain of the tight rubber bands or of the intense heating of the tissues. Nor can the rise in temperature be due to substances liberated in the heated tissues and transported in the blood-stream to the sympathetic centres, as such a mechanism would necessitate the rapid appearance of a rise in temperature after cessation of the blockade.

Table 1.

*Indirect heating in 10 normal subjects without and with simultaneous occlusion of the circulation from the upper limbs for 10—15 minutes. Besides the latent periods found the toe-pulp temperatures are given at the beginning of heating and just before the end of the blockade.*

Experiment no.	Indirect heating with normal circulation		Indirect heating with simultaneous occlusion of the circulation for the first 10—15 min.			
	Toe pulp temperature at the beginning of the heating in °C.	Latent period in min.	Toe pulp temperature at the beginning of heating in °C.	Duration of blockade in min.	Toe pulp temperature at the end of blockade in °C.	Time for rise in pulp temperature from the end of blockade in min.
1 .....	17.1	10	17	15	12.6	12
2 .....	19.6	8	19.6	10	16.2	9
3 .....	20	7	21	10	19.2	>15
4 .....	20	10	22	10	20.4	3
5 .....	24.4	4	22.2	15	21.6	6
6 .....	20.6	4	20.6	10	18.2	5
7 .....	17.6	7	19.8	10	17.2	7
8 .....	21.4	7	18.6	12	16.4	6
9 .....	21.2	7	20.4	12	17.8	6
10 .....	15.8	12	16	15	13.8	>12

Table 2.

*Heating of both hands without and with cooling of the vessels of the neck. The latent period from the beginning of heating and till increase in toe-pulp temperature occurs is given in minutes.*

Experiment no.	Latent period without cooling in minutes	Latent period with cooling in minutes
1 .....	4—6	8
2 .....	6	11
3 .....	6	10
4 .....	9	> 20
5 .....	4	> 25
6 .....	7	> 25
7 .....	15	> 45

The rise in temperature must therefore be due to the heat supplied to the body or to the summation of nervous impulses from a large heated area. Both these possibilities would require a certain period of heating under normal circulatory conditions. To determine which of them is correct, a series of experiments has been carried out in which one hand is heated at the same time as the forearm of the same or opposite side is cooled, and again in which both hands are heated at the same time as cooling is applied to the great vessels of the neck.

When one hand is warmed simultaneously with cooling of the forearm of the same side the rise in temperature of the toes fails to appear or is considerably delayed in comparison with the latent period observed in the absence of simultaneous cooling. Cooling of the opposite forearm does not affect the onset of the rise in temperature of the toes. The observed inhibition cannot therefore be the result of vaso-constrictor impulses to the lower limbs produced by the cooling, as in such case the effect would be identical when symmetrical areas are cooled. The

Table 3.

*Latent period and the rise in temperature per minute in 28 experiments upon 5 different subjects after heating the finger tips, one hand or two hands. The toe-pulp temperature is given for all experiments at the beginning of heating and at the occurrence of rise in pulp-temperature.*

Subject	Toe pulp temperature at the beginning of heating in ° C.	Latent period	Toe pulp temperature at the beginning of the temperature rise in ° C.	Rise in temperature per min in ° C.
heating of 2 hands				
D. 1 .....	14.8	6	14.0	5.8
A. 2 .....	16.8	5	16.8	3.0
E—J. 3 .....	17.0	6	15.4	2.4
S. 4 .....	18.2	7	17.8	2.0
	18.2	6	17.0	2.0
	17.6	6	17.4	2.1
	20.0	6	18.0	2.6
F. 5 .....	21.4	3	20.4	1.6
	21.0	6	18.8	2.4
	18.0	3	17.6	4.5
	17.5	6	16.0	2.0
	19.0	6.5	17.0	2.0
	17.0	6	16.4	2.0
heating of 1 hand				
D. 1 .....	16.2	13	13.2	0.7
A. 2 .....	17.0	11	16.0	0.9
E—J. 3 .....	16.4	9	15.4	1.9
S. 4 .....	16.2	8	16.0	2.0
	21.0	9	19.2	1.8
F. 5 .....	20	15	15.2	1.2
	20.5	16	14.9	1.5
	21.0	25	14.6	0.9
	20.0	25	14.6	0.9
heating of fingertips				
D. 1 .....	19.0	23	15.2	0.30
A. 2 .....	16.8	18	13.8	0.26
E—J. 3 .....	17.6	11	17.2	1.60
S. 4 .....	21.0	20	17.6	0.40
	22.4	17	17.6	1.5
F 5 .....	19.4	20	14.4	0.1



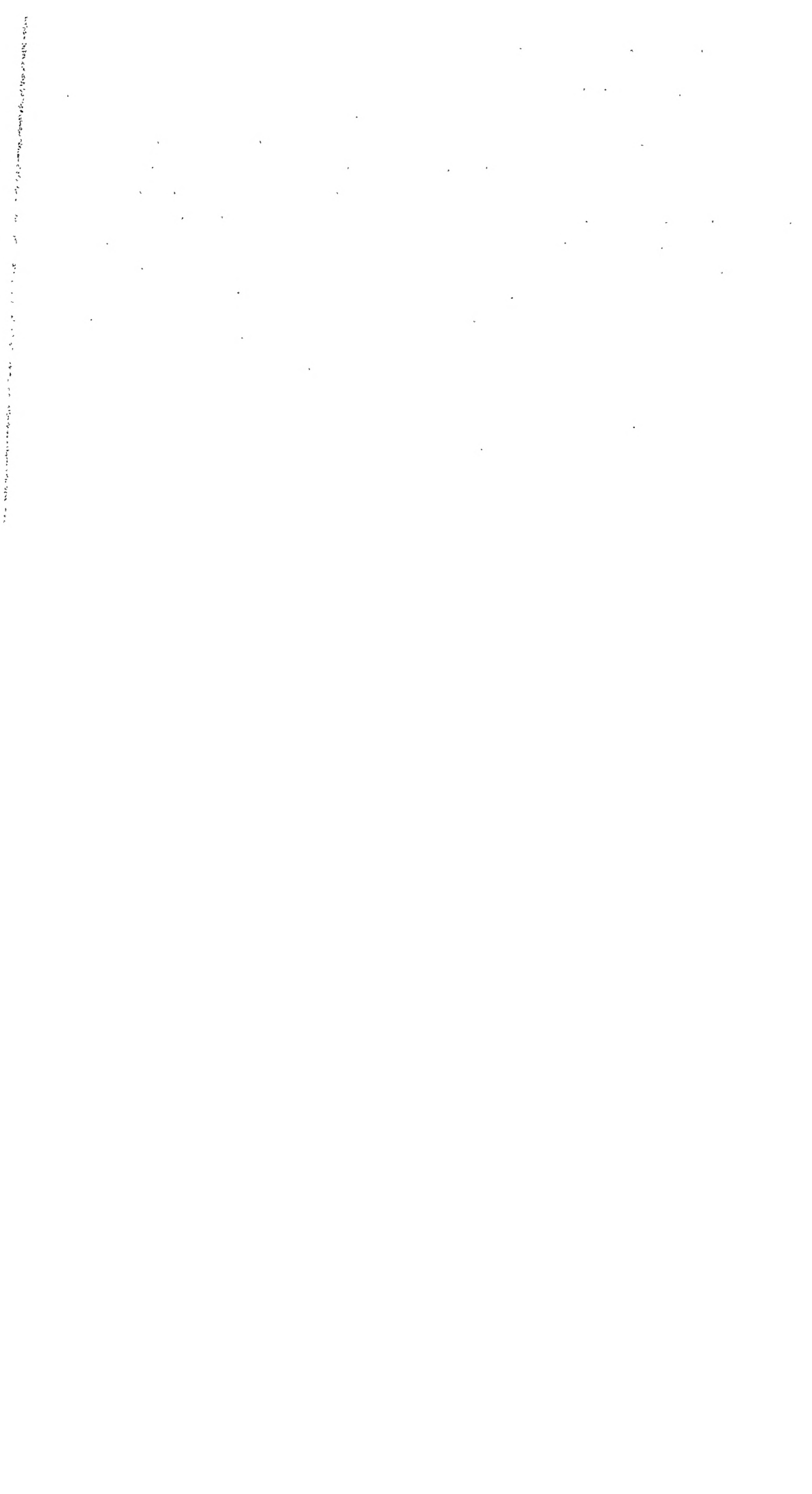
inhibition must therefore in all probability be due to the dissipation of a material part of the assimilated heat from the blood stream from the warmed areas before it reaches the trunk. A summative effect caused by the heating is less probable, since cooling does not lead to a vaso-constrictor effect. To elucidate the question further, cooling of the vessels of the neck was carried out simultaneously with heating of both hands. A vaso-dilatation due to summation of neurogenic impulses from the whole arm should be released in this case irrespective of the cooling. The results are given in table 2, showing the latent period in 7 subjects during heating of the hands with or without cooling. It can be seen that the cooling inhibits or greatly retards the rise in temperature in all experiments.

The rise in temperature observed with this technique must therefore be due to the assimilation of heat by the body. Hence it is natural to suppose that the release of the reaction and the rate at which the temperature rises are dependent upon the area of tissue warmed. How far this is the case has been investigated in five subjects by warming the fingers of one or both hands. The results are presented in table 3. It appears that the latent period is both shortest and most uniform from one person to another when both hands are warmed, and in the same subject is most constant under such circumstances. The rate of rise of temperature increases with the amount of tissue heated, but even under uniform experimental conditions there are great variations between one subject and another, and between repeated experiments on the same subject. No relation can be shown, either between the pulp temperature at the beginning of heating and the latent period, or between the temperature at the onset of the rise and the rate of increase.

These experiments suggest that nervous impulses graduated according to the rate of heating are generated in heat-sensitive areas as soon as a heat-threshold is exceeded. The level of this threshold varies from one subject to another. In the present investigation, comprising 25 subjects, the latent period when both hands were warmed varied between three and fifteen minutes. In the single subject the latent period is remarkably constant.

### Discussion.

The experiments show that the indirect heating produced in the toes is due to the heat assimilated through the hands and not to nervous impulses. This divergence from the results obtained by Duthie and Mackay must be due to the indirectly heated parts being subjected to cooling in our experiments, since the other experimental conditions were identical in the two investigations. Especial stress was laid upon working at corresponding temperatures of the room and the toe pulp during the heating. Because of the cooling device the loss of heat from the indirectly warmed areas and thereby from the whole body is greater in our experiments. Therefore an increased circulation to the toes is necessary to produce a rise in temperature, but on account of the greater heat-loss from the whole body there will occur a reduction of the circulation, if heat is not simultaneously supplied, probably due to a centrally released emission of vaso-constrictor impulses. (Ferris et al. 1947). Furthermore it is possible that a vaso-constriction produced.



used to demonstrate pathological conditions the mode of action upon the sympathetic nervous system has been investigated.

It is shown that the temperature increase is released by the action of heat. The neurogenic release demonstrated by Duthie and Mackay (1940) using the original technique of Gibbon and Landis can therefore be assumed to take place only when the loss of heat from the body, and particularly from the indirectly heated areas, is small. When smaller areas are heated the latent period decreases, and the rate at which the temperature rises accelerates with enlargement of the amount of warmed tissue.

This indicates that the heat-sensitive centre can send out graduated impulses dependent upon the rate of supply of heat, after a certain threshold has been exceeded. When both hands are warmed the latent period is constant in the same subject, because the loss of heat is insignificant in comparison with the simultaneous heat absorption. With direct warming of both hands 3—15 minutes elapse before the temperature of the toe pulp rises. It follows from this that small deviations from the normal value in the single subject are impossible to demonstrate. A prolonged latent period may be due to changes in the peripheral vessels of the extremities, in the sympathetic pathways from the heat sensitive cells to the vessels, or may have a central causation. The localisation of a demonstrated pathological change may therefore necessitate supplementary investigations by other methods.

#### References.

- Arnott, W. M. & J. M. Macfie: *J. Physiol.* 1948, *107*, 233. — Christiansen, S., M. Fog & T. Vanggaard: *Acta Psychiat. Neurol.* 1939, *14*, 413. — Duthie, J. J. R. & R. M. G. Mackay: *Brain* 1940, *63*, 295. — Ferris, B. G., R. E. Foster, E. L. Pillion & W. R. Christensen: *Am. J. Physiol.* 1947, *150*, 304. — Gibbon, J. H. & E. M. Landis: *J. Clin. Invest.* 1932, *11*, 1019. — Lewis, T. & G. W. Pickering: *Heart* 1931, *16*, 33. — Pickering, G. W.: *Heart* 1932, *16*, 115. — Sewall, H. & E. Sanford: *J. Physiol.* 1890, *11*, 179. — Skouby, A. P.: *Acta Med. Scand.* 1949, *134*, 335. — Stewart, G. N.: *Heart* 1911, *3*, 76. — Uprus, V., J. B. Gaylor & E. A. Carmichael: *Clin. Sci.* 1936, *2*, 301. — Vanggaard, T.: *Arteriovenose Anastomoser i Ekstremiteterne*. Thesis, Copenhagen 1941.
-

### Book Review.

Lea Rossi Del Bo: Il Sistema nervoso studiato con una nuova tecnica. 83 p. 196 fig. Officina d'arte grafica A. Lucini & C., Milan 1949.

This publication consists mainly of a number of photographs, excellent in themselves, accompanied by a scanty text in Italian.

The authoress's technique consists in fixing the preparation in Cox's solution followed by washing in aq. dest. After freezing and sectioning, the preparation is washed for 48 hours in aq. dest. It is then placed in an about 2 % solution of nitrate of silver for 24—48 hours (temp. + 18° — 22° C). The preparation is subsequently treated with alcohol, xylol, and finally, mounted in the usual manner.

With great diligence the author has thus treated a large number of preparations from the central nervous system and different parts of the peripheral nervous system. She has also investigated cartilage, tumours and finally, brain from the mentally diseased.

The staining of nervous elements is probably one of the most difficult fields of histological technique, where not only is the technical procedure difficult, but great claims are also laid on the person carrying out the staining. Finally, the investigator's own judgement and critical sense is severely tried.

As far as I can understand, the present work is an outstanding example of whither uncritical enthusiasm may lead. At the same time a strong light is thrown on the difficulties in the study of the nervous apparatus, especially by the silver method.

The observations are new, in so far as they do not tally with what earlier research workers have found with silver or other nerve staining. The angular, surrealistic course of the authoress's nerve fibres ought to have made her hesitate (figs. 12, 20). Still more ought her judgement to have seen the red light in the presence of pictures 58—69. She considers that the black, angular, rectilinearly defined figures with similar offshoots are ganglion cells. In the opinion of the present reviewer they exhibit a great resemblance to crystals or precipitations of some kind, possibly on the basis of nervous elements. The authoress's finding of nerve fibres in cartilage ought also to have given her pause, in any case attempts with other nerve staining would appear to be appropriate here, as no one has previously found either nerves or vessels in cartilage. The abundance of nervous structures which the authoress considered she reveals is therefore extremely remarkable.

In the beautifully illustrated work it is completely hopeless to try to decide which formations are nerves and which are artefacts. The method must first be re-examined and further modified before it becomes serviceable for nerve stainings. As things are now, the work appears to the present reviewer to constitute nothing more than an example of where the difficulties in histological technique can lead an uncritical practitioner.

*Hjalmar Holmgren.*

### Book Review.

»Über die Anzeigepflicht des Prosektors wegen ärztlichen Verschuldens«, von F. Feyrter, o. Professor der Pathologie, Verlag Wilhelm Maudrich, Wien 1949.

Die Publikation behandelt die Anzeigepflicht des *Prosektors wegen ärztlichen Verschuldens* und stellt hauptsächlich eine Verteidigungsschrift des Verfassers dar, welcher als o. Professor der Pathologie der Univ. G. 1946 einem Gerichtsverfahren unterworfen, verhaftet und seines Dienstes entledigt wurde. Verf. stand als Prosektor unter dem Verdacht des Missbrauches der Amtsgewalt infolge Unterlassung der Anzeige von Todesfällen, die den aus Deutschland berufenen früheren Professor der Frauenheilkunde in G. schwer belastet haben sollen. Verf. setzt sich ausführlich mit den ziemlich verwickelten Bestimmungen des österr. Strafgesetzes über den Begriff des ärztlichen Verschuldens auseinander und betont, dass der Prosektor weder Besserwisser noch Richter ist und seine Anzeigepflicht einzig und allein auf *kriminelles* ärztliches Verschulden beschränkt bleibt. Verf. beschuldigt den früheren Gerichtsmediziner in G., nunmehr Chef in W., des »gerichtsärztlichen Kunstfehlers« in Erstattung des Gutachtens in seiner Sache, wobei er sich auf die günstige Stellungnahme zahlreicher österr. Pathologen stützt.

Das kleine Buch illustriert für jedes Land die Notwendigkeit, eine zentrale medizinische Aufsichtsbehörde mit staatlicher Vollmacht zu besitzen, welche nach den Richtlinien modernen medizinischen Wissens allein zu entscheiden hat, ob gegen einen Arzt eine Anklage zu erheben ist. Nur dadurch wird verhindert, dass wie im vorliegenden Fall ein Arzt Gegenstand eines peinlichen Gerichtsverfahrens wird, welches sich nicht selten auf böswillige Laienanzeigen oder Unkenntnis von Seiten der Behörden gründet.

*Philipp Schneider.*

---

# Acta Medica Scandinavica.

## Index to Supplementary Volumes 201—235.

- CCI. *Herman Hortling*: The influence of electric shock and adrenalin injections on the leukopoiesis and the erythropoiesis. — 1948.
- CCII. *Ake Edlén*: Pathophysiology of peptic ulcer. — 1948.
- CCIII. *Gösta Ekehorn*: Sherrington's »Endeavour of Jean Fernel» and »Man on his nature». — 1948.
- CCIV. *Astrid Fagraeus*: Antibody production in relation to the development of plasma cells. — 1948.
- CCV. *Gunnar Wihman*: A contribution to the knowledge of the cellular content in exudates and transudates. — 1948.
- CCVI. Comptes rendus du vingtième congrès de médecine interne des pays du Nord, réuni à Gothembourg du 27 au 29 Juin 1946. — 1948.
- CCVII. *J. G. Borst*: The maintenance of an adequate cardiac output by the regulation of the urinary excretion of water and sodium chloride; an essential factor in the genesis of oedema. — 1948.
- CCVIII. *Jóhann Saemundsson*: Potassium concentration in human gastric juice. — 1948.
- CCIX. *Karl Erik Grevin*: Some supplementary leads in clinical electrocardiography. — 1948.
- CCX. *Fried Nilsson*: Anemia problems in rheumatoid arthritis. — 1948.
- CCXI. *Börje Ejrup*: Tonoscillography after exercise. — 1948.
- CCXII. *Ilmari Paronen*: Reiter's disease. — 1948.
- CCXIII. *Einar Meulengracht*, in honorem. — 1948.
- CCXIV. *Axel Ström*: Examination into the diet of norwegian families during the war-years 1942—45. — 1948.
- CCXV. *Holger Wahlund*: Determination of the physical working capacity. — 1948.
- CCXVI a. *Olle Hogeman*: Clearance tests in renal disorders and hypertension. — 1949.
- CCXVI b. *Olle Hogeman*: Renal function in diabetic nephropathy. — 1949.
- CCXVII. *Nils Söderström*: Myocardial infarction and mural thrombosis in the atria of the heart. — 1949.
- CCXVIII. *Hall Scharlum-Hansen*: The sternal marrow function, with special reference to erythropoiesis, in pernicious anaemia. — 1949.
- CCXIX. *Ake E. Nyström*: Health hazards in the chloroprene rubber industry and their prevention. — 1949.
- CCXX. *Gerhard Larsen*: The distribution of red blood cell diameters in liver diseases. — 1949.
- CCXXI. *Georg-Fredrik Saltzman*: The origin of blood-platelets. — 1949.
- CCXXII. *Ragnar Müller*: Studies on disseminated sclerosis, with special reference to symptomatology, course and prognosis. — 1949.
- CCXXIII. *Ernst Hammarström*: Phage-typing of *Shigella Sonnei*. — 1949.
- CCXXIV. *Folke Möller*: The occurrence of post infectious nervous complications and allied disorders in Sweden. — 1949.
- CCXXV. *Olof E. Sandler*: Some experimental studies on the erythropoietic effect of yellow bone marrow extracts and batyl alcohol. — 1949.
- CCXXVI. *Gunnar Björck*: On myoglobin and its occurrence in man. — 1949.
- CCXXVII. *Carl-Axel Adamson*: A bacteriological study of lymph nodes. — 1949.
- CCXXVIII. *Gösta Rooth*: Inhalation of liquid aerosols. — 1949.
- CCXXIX. *Nils Alwall*: On the artificial kidney VIII—XIII. — 1949.
- CCXXX. *Lars Emil Tøtterman*: Vitamin C and iron metabolism. — 1949.
- CCXXXI. *Gösta Ekehorn*: Sherrington's »Endeavour of Jean Fernel» and »Man on his nature». — 1949.
- CCXXXII. *Folke Möller*: On postinfectious nervous involvement and related disorders of spontaneous origin. — 1949.
- CCXXXIII. *Alf Tellefsen*: Über die Rheumatismusmorbidity durch Krankenkassenmaterial beleuchtet. — 1949.
- CCXXXIV. Papers dedicated to Dr. *Poul Iversen* on his sixtieth birthday November 20, 1949. — 1950.
- CCXXXV. *Bengt Skanse*: Radioactive iodine in the diagnosis of thyroid disease. — 1950.